Discriminative stimulus effects of cocaine in female versus male rats

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Abstract

Eight female and 8 male rats were trained to discriminate 5.6 mg/kg i.p. cocaine from saline on a 2-lever, food-reinforced drug discrimination procedure. Female rats acquired the cocaine discrimination in approximately the same number of sessions that males did (43 ± 7 vs. 51 ± 9 sessions, respectively), and the ED50 for cocaine discrimination was nearly equivalent in female and male rats (2.46 ± 0.41 vs. 2.32 ± 0.49 mg/kg, respectively). The time course for cocaine discrimination was similar in female and male rats, except the offset of cocaine's effects occurred significantly earlier in females than in males. D-Amphetamine dose-dependently substituted for cocaine in all 7 males and 6 of 7 females tested, with no significant sex difference in the ED50 values for d-amphetamine substitution. None of the three opioid agonists tested, morphine (μ), U69,593 (κ) or BW373U86 (δ), fully substituted for cocaine in rats of either sex. The dopamine antagonist fluphenazine blocked the discriminative stimulus effects of cocaine to approximately the same extent in both sexes. Further drug discrimination training with a higher dose of cocaine, 10 mg/kg, did not significantly alter the ED50 for cocaine discrimination, and there was still no significant sex difference in ED50 values (3.50 ± 0.39 vs. 2.36 ± 0.41 mg/kg in females vs. males, respectively). In these same rats, however, cocaine (1–10 mg/kg) produced significantly greater locomotor activation in females than in males on a test of spontaneous locomotor activity. Thus, these results suggest that there are few sex differences in discriminative stimulus effects of cocaine, even at doses that produce significantly different locomotor responses in female versus male rats.

Keywords: Drug discrimination; Cocaine; Sex differences

1. Introduction

Across nearly all licit and illicit drug classes, men are more likely than women to use, abuse and be dependent on drugs (Anthony and Helzer, 1991; NIDA, 1993; Johnston et al., 1994a,b). It is not known whether this 'gender gap' in drug-taking behavior reflects biological differences in reinforcing and subjective effects of drugs. However, a number of biological factors are known to contribute to sex differences in drug effects, including differential metabolism, body weight, body fat content, and gonadal hormones (Owens and Hume, 1994; Harris et al., 1995; Yonkers and Hamilton, 1995). Additionally, central dopamine transmission, a primary neural substrate of drug reinforcement (Koob, 1992; Wise et al., 1992) differs between female and male rodents (Castner et al., 1993; Dorce and Palermo-Neto, 1994). Thus, it is possible that sex differences in such dopaminergic 'reward circuitry' may underlie gender differences in drug-taking behavior.

In a rare controlled study of sex differences in drug effects, Chait (1994) reported that men chose a mild stimulant (ephedrine) more frequently than women and showed a more positive mood response to the drug. Among animal studies, there are also some reported sex differences in psychostimulant effects. For example, female rats self-administered i.v. cocaine to higher breaking points than males did (Roberts et al., 1989). However, although adult female rats also responded at higher rates than males for electrical brain stimulation of the medial forebrain bundle (Cohen and Lieblich,
directly compared to its locomotor effects in the present study. Finally, because cocaine may affect gonadal hormone status in females (Mello et al., 1990; King et al., 1993) and thereby influence sex differences in behavior, estrous cyclicity was assayed cytologically for 1 week at the beginning and end of the study, to determine whether this regimen of cocaine administration substantially altered estrous cyclicity.

2. Subjects and methods

2.1. Subjects

Subjects were experimentally naive male and female Sprague-Dawley rats, ~ 3 months old at the beginning of the experiment. Rats were singly housed to maintain them at ~ 85% of free-feeding body weight throughout the study. Males and females were housed in separate, adjacent rooms. Rats were fed ~ 2 h post-session Mondays through Thursdays, with a bulk feeding on Friday for the weekend; water was available ad libitum. Vivarium conditions were 72°F average temperature, and a 12:12 h light:dark cycle, lights on at 07:00 h.

2.2. Apparatus

Drug discrimination training and testing were conducted in standard, sound-attenuated, two-lever operant chambers (Med Associates, St. Albans, VT). Half of the chambers were designated for males only and half were designated for females only. Levers were 7 cm above the chamber floor, equidistant from the central food hopper, and required ~ 30 g of force to register a response. A light above each lever, and houselight on the wall opposite the levers signalled session duration. All sessions were controlled and data collected by microcomputer.

Locomotor activity screening was conducted in 40 x 20 x 23 cm clear Plexiglas rodent cages, each placed within a photobeam apparatus (Opto-varimex, Columbus Instruments, Columbus, OH) with a white noise background. The 15 photobeams that crossed the width of each cage were 2.5 cm apart, and 8 cm above the cage floor.

2.3. Procedure

2.3.1. Drug discrimination

Rats were trained to lever-press for 45-mg pellets (Noyes, Lancaster, NH) on an FR-1 schedule; the response requirement was gradually increased to an FR-10 schedule. When responding on both levers was reliable, cocaine (5.6 mg/kg) or saline was then administered i.p. 15 min pre-session on a pseudo-random, 5-day/week schedule, such that drug and saline were each administered at least twice a week and not more
than twice in a row. Half of each sex was reinforced for responding on the right lever after cocaine administration, and the other half was reinforced for responding on the left lever after cocaine administration. Once rats were reliably discriminating cocaine from saline (9 of 10 consecutive sessions with \( \geq 90\% \) of total responses on the correct lever and \( \leq 5 \) responses on the incorrect lever prior to completion of the first FR), substitution tests were conducted every Tuesday and Friday as long as the most recent cocaine and saline training sessions were correct. During substitution tests, responding on both levers was reinforced. Training sessions were continued on Mondays, Wednesdays and Thursdays. Both training and test sessions were 20 min long.

Substitution curves were obtained in the following order: cocaine, D-amphetamine, morphine, BW373U86 and U69,593. The time course of cocaine discrimination was then determined by administering 5.6 mg/kg cocaine and then testing rats for 5-min sessions 5, 15, 30, 60 and 120 min post-injection. The 1-min time point was obtained on a different test day; 5.6 mg/kg cocaine was administered and rats were tested for 5 min only, 1 min post-injection. Cocaine locomotor activity tests were then conducted (on Tuesdays and Fridays, instead of the drug discrimination session). Then on the discrimination task, two doses of fluphenazine were tested in combination with saline and cocaine (1–18 mg/kg), and then the cocaine substitution curve was redetermined. The cocaine training dose then was increased to 10.0 mg/kg. Once rats met training criteria at this higher dose (9 of 10 consecutive sessions with \( \geq 90\% \) of total responses on the correct lever and \( \leq 5 \) responses on the incorrect lever prior to completion of the first FR), the cocaine dose-effect curve was redetermined a third time. For a subset of females (\( N = 3 \)), estrous cyclicity was determined cytologically by vaginal lavage during the first and last weeks of testing.

### 2.3.2. Spontaneous locomotor activity

Rats were administered either cocaine or saline i.p., and 15 min later placed in the locomotor activity apparatus. Horizontal activity was measured as the number of photobeam breaks in the subsequent 60 min. Drug discrimination rats were tested with saline and 5 doses of cocaine (different order of dosing for each rat) on Tuesdays and Fridays during their usual test time; drug discrimination training sessions were continued on Mondays, Wednesdays and Thursdays. Age-matched cocaine naive rats were screened in the same manner following a single, acute dose of cocaine or saline; that is, cocaine-naive rats were tested with only 1 dose of cocaine or saline, instead of all 4 dose conditions.

### 2.4. Drugs

Cocaine hydrochloride (National Institute on Drug Abuse, NIDA), morphine sulfate (Mallinckrodt), BW373U86 (gift of Burroughs Wellcome Co.), D-amphetamine (Sigma), and fluphenezine (Sigma) were dissolved in physiological saline (0.9% NaCl). U69,593 (NIDA) was dissolved in 85% lactic acid to which saline was added; the pH was adjusted to 5.5 with 1 N NaOH. All injections were given in a volume of 1.0 ml/kg. Cocaine and BW373U86 were administered i.p., and all other drugs were administered s.c.

### 2.5. Data analysis

Percent drug-lever responding and response rate were recorded daily. For each rat, the estimated dose at which substitution was 50% and/or response rate was 50% of saline control rate (ED\(_{50}\)) was determined by linear regression, using one data point above 50% and one point below 50%. 'Complete substitution' was defined as \( \geq 80\% \) total responses on the drug lever, 'partial substitution' was defined as \( \geq 20\% \) but \(< 80\% \) total responses on the drug lever, and 'no substitution' was defined as \(< 20\% \) total responses on the drug lever. Student's t-test was used to compare males and females on number of sessions to meet training criteria, response rates and locomotor activity after saline, and all ED\(_{50}\) values. Two-way, repeated measures ANOVA tests (Sex \( \times \) Dose) were used to determine whether sex differences in drug effects on response rate and spontaneous locomotor activity were statistically significant. A two-way ANOVA (Sex \( \times \) Dose) was used to analyze differences in spontaneous locomotor activity among cocaine-naive rats administered a single dose of cocaine. When significant sex by dose interactions were obtained, Student-Newman-Keuls post-hoc tests were used to identify at which dose(s) there was a sex difference. Significance level for all analyses was set at \( P \leq 0.05 \).

### 3. Results

#### 3.1. Training

Females acquired the 5.6 mg/kg cocaine discrimination at a slightly but not significantly faster rate than males did. The mean \( \pm\) S.E.M. number of discrimination training sessions to meet testing criteria was 43.0 \( \pm\) 6.5 for females and 51.0 \( \pm\) 8.8 for males (\( t_{14} = 0.73, \) n.s.).
3.2. Substitution testing

Fig. 1 (left panel) shows that sensitivity to the cocaine discriminative stimulus was highly similar in female and male rats; there were no sex differences in ED_{50} values for cocaine substitution (Table 1) (t_{14} = -0.12, n.s.). Mean response rates after saline administration also were nearly identical in females and males (0.70 ± 0.06 vs. 0.69 ± 0.07 responses/s, respectively; t_{14} = 0.06, n.s.). Females responded at higher rates than males after 5.6 and 10 mg/kg cocaine; however, there was no main effect of sex on response rate, and a marginal sex by dose interaction (Sex: F_{1,14} = 1.44, n.s.; Dose: F_{4,56} = 2.80, P = 0.04; Sex × Dose: F_{4,56} = 2.36, P = 0.06).

Fig. 2 shows the time course of 5.6 mg/kg cocaine substitution in female and male rats. Complete substitution occurred by 1 min post-injection, and the offset of drug effect occurred 60–120 min post-injection. There was no overall sex difference. However, there was an interaction between time and sex (F_{5,69} = 2.37, P = 0.05): at the 60-min time point, females made significantly fewer cocaine-appropriate responses than males did.

Fig. 1 (second panel) shows that another psychostimulant, D-amphetamine, substituted for cocaine in a dose-dependent manner in both female and male rats. Again, there was no overall sex difference in ED_{50} values: the average ED_{50} for D-amphetamine substitution was 0.30 ± 0.10 mg/kg in females and 0.26 ± 0.05 mg/kg in males (t_{1} = 0.436, n.s.). D-Amphetamine completely substituted for cocaine in all 7 males at 1.06 mg/kg, but completely substituted in only 5 of 7 females at this dose; the other 2 females were tested with a higher dose, 1.0 mg/kg, which substituted in 1 female but not in the other (although it did decrease response rate to ~50% of control in this rat). Rates of responding were not significantly altered within the dose range of D-amphetamine shown in Fig. 1, and females responded at slightly but not significantly higher rates than males across these doses (Sex: F_{1,12} = 0.34, n.s.; Dose: F_{3,36} = 0.68, n.s.; Sex × Dose: F_{3,36} = 0.26, n.s.).

Fig. 1 (middle and right panels) also shows substitution patterns and response rate-altering effects of 3 opioid agonists in cocaine-discriminating females and
males. The μ agonist morphine did not substitute for cocaine in a dose-dependent manner in either sex, but decreased response rate dose-dependently in all rats (Sex: $F_{1,10} = 0.26$, n.s.; Dose: $F_{3,30} = 39.31$, $P < 0.001$; Sex × Dose: $F_{3,30} = 1.52$, n.s.). The δ agonist BW373U86 also did not substitute for cocaine in a dose-dependent manner in either sex. Within the dose range tested, BW373U86 decreased response rates slightly but not significantly more in females compared to males (Sex: $F_{1,8} = 2.68$, $P = 0.14$; Dose: $F_{3,16} = 5.06$, $P = 0.02$; Sex × Dose: $F_{2,16} = 1.45$, n.s.); due to a limited drug supply, higher doses were not tested. The κ agonist U69,593 also did not fully substitute for cocaine in all rats of either sex. However, following 0.1 mg/kg U69,593, 2 of the 4 males that responded at this dose (of 5 tested) responded exclusively on the cocaine-appropriate lever, whereas no females responded on the cocaine-appropriate lever at any dose of U69,593. U69,593 decreased response rate in a dose-dependent manner in all rats (Sex: $F_{1,9} = 0.86$, n.s.; Dose: $F_{3,16} = 33.08$, $P < 0.001$; Sex × Dose: $F_{2,16} = 0.75$, n.s.).

### 3.3 Antagonism of the cocaine discriminative stimulus

Fig. 3 shows the dopamine antagonist fluphenazine tested in combination with saline (0 mg/kg) or cocaine (1–18 mg/kg). Fluphenazine + saline did not substitute for cocaine in either sex, although it decreased response rate in a dose-dependent manner in both sexes. When administered in combination with cocaine, fluphenazine dose-dependently shifted the cocaine dose-effect curve to the right in both sexes: the low and high doses of fluphenazine increased cocaine ED$_{50}$ values approximately 0.34 and 0.53 log units, respectively, in female rats, and 0.18 and 0.50 log units, respectively, in males (Table 1). A statistical comparison of the ED$_{50}$ values for cocaine substitution alone and in combination with fluphenazine revealed no sex differences (Sex: $F_{1,13} = 0.40$, n.s.; Dose of fluphenazine: $F_{2,20} = 31.53$, $P < 0.001$; Sex × Dose: $F_{2,20} = 0.86$, n.s.).

### 3.4 Effects of cocaine on spontaneous locomotor activity

Fig. 4 shows the effects of cocaine on spontaneous locomotor activity in female and male drug discrimination rats. There were no sex differences in locomotor activity following saline ($t_{10} = 0.44$, n.s.). Cocaine increased locomotor activity in both sexes, but females showed greater locomotor activation than males did at the higher doses (Sex: $F_{1,10} = 5.55$, $P = 0.04$; Dose: $F_{3,30} = 6.13$, $P = 0.002$; Sex × Dose: $F_{3,30} = 3.81$, $P = 0.03$). To determine whether cocaine drug discrimination rats may have become sensitized to cocaine's locomotor activating effects during training, cocaine's locomotor effects were tested in a separate group of cocaine-naive rats. In these rats, acute cocaine also significantly increased locomotor activity, but females showed only marginally greater increases than males (Sex: $F_{1,18} = 4.09$, $P = 0.06$; Dose: $F_{2,18} = 4.99$, $P = 0.02$; Sex × Dose: $F_{2,18} = 1.12$, n.s.). Table 2 shows cocaine's locomotor effects in cocaine-discriminating vs. cocaine-naive rats.

### 3.5 High dose cocaine discrimination

Redetermination of the cocaine discrimination dose-effect curve following all substitution and locomotor tests yielded curves that were highly similar to the initial curve (data not shown); Table 1 shows that over the course of the study, the mean ED$_{50}$ value for rats discriminating 5.6 mg/kg cocaine increased 0.15 log units in females, and decreased 0.11 log units in males. Thus, there was still no sex difference in ED$_{50}$ values at the end of the study ($t_{13} = 1.63$, n.s.). Response rates after saline were also approximately the same as at the beginning of the study, for both females and males (0.66 ± 0.11 and 0.60 ± 0.12 responses/s, respectively; $t_{13} = 0.39$, n.s.). Females also still responded at slightly but not significantly higher rates than males after cocaine (Sex: $F_{1,13} = 1.13$, n.s.; Dose: $F_{4,52} = 2.22$, $P = 0.08$; Sex × Dose: $F_{4,52} = 0.06$, n.s.).
To determine whether sex differences might exist with a higher, more commonly used training dose of cocaine, some female and male rats were subsequently retrained to discriminate 10 mg/kg from saline. Again, females and males met training criteria in approximately the same number of sessions (13.3 ± 1.8 vs. 14.7 ± 2.9 sessions, respectively), and the ED₉₀ values for cocaine substitution were not statistically different between females and males (t₁₀ = -2.04, P = 0.07; Table 1).

3.6. Effect of cocaine on estrous cyclicity

The 3 female rats that were screened for estrous cyclicity each showed at least 1 day of proestrus, estrus and diestrus (in that order) during the 7 consecutive sampling days, both at the beginning and end of the experiment. No gross abnormalities in vaginal cell morphology were observed.

Fig. 3. Effects of the DA antagonist fluphenazine on the discriminative stimulus (top panels) and response rate effects (bottom panels) of cocaine in female and male rats trained to discriminate 5.6 mg/kg cocaine from saline. Fluphenazine (or saline) was administered in mg/kg s.c., 60 min pre-session, followed by saline (0) or cocaine (1.0–18 mg/kg) i.p., 15 min pre-session. Each point represents the mean ± 1 S.E.M. of 5–7 rats.

Fig. 4. Locomotor activity on a spontaneous locomotor activity test following saline or cocaine in female and male rats trained to discriminate 5.6 mg/kg cocaine from saline. Saline or cocaine was administered i.p., 15 min pre-test, twice/week (different dose order each rat) until all 5 doses were completed in each rat. Each point represents the mean ± 1 S.E.M. of 6 rats. *P ≤ 0.05, Student-Newman-Keuls test.
4. Discussion

In the present study, there were few sex differences in cocaine discrimination in the rat, across a number of parameters. The average number of sessions to acquire a cocaine discrimination, the ED$_{50}$ for and time course of cocaine substitution, the pattern of substitution with other agonists, and antagonism by fluphenazine were all nearly equivalent between female and male rats. In contrast, there were robust sex differences in cocaine's locomotor activating effects in the same rats.

The general pattern of the results obtained in female and male rats agrees with previous cocaine discrimination studies conducted in male rats. For example, previous studies indicate that the mean number of sessions to meet training criteria using an intermediate dose of cocaine (4–5 mg/kg) was ~39–42 sessions, using criteria similar to or slightly less stringent than those used in the present study (e.g. Callahan et al., 1992; Rapoza, 1993). Additionally, the ED$_{50}$ for cocaine substitution in the present study (~2.4 mg/kg) is within the range reported previously for males trained to discriminate an intermediate dose of cocaine (~1.3–3.4 mg/kg: Callahan et al., 1992; Rapoza, 1993; Fowler et al., 1993). Female rats in the present study did respond at higher rates than males after the 2 highest doses of cocaine, but given the marginally significant difference across all 5 doses of cocaine, it is difficult to assess whether this sex difference is a functionally important one.

Previous reports in male rats or squirrel monkeys discriminating cocaine from saline indicate a time course of cocaine discrimination highly similar to that found in the present study (onset by 5 min post-injection, offset at 60–120 min: Gauvin et al., 1990; Katz et al., 1991; Heyser et al., 1994). The offset of cocaine's discriminative effects occurred ~30 min earlier in females than in males. It has been reported previously that brain/plasma levels of cocaine correspond fairly closely to its subjective and locomotor effects in male animals (Rennick et al., 1987; Iau et al., 1991; Lamas et al., 1995). Thus, the fact that females showed less cocaine-appropriate responding at 60 min post-injection suggests that brain levels of cocaine may be lower in females than in males at that time. However, Heyser et al. (1994) reported significantly higher cocaine levels in the brains of Sprague–Dawley female rats compared to males (main effect measured 5–60 min post-injection), which does not support such a pharmacokinetic hypothesis. Thus, the sex difference in the time course of cocaine discrimination found in the present study may not simply reflect sex differences in pharmacokinetics but may be related to minor sex differences in, for instance, dopamine receptor pharmacology.

Patterns of agonist substitution in the present study are also in general agreement with those of previous studies in male rats. For example, D-amphetamine has been shown to fully substitute for cocaine in rats discriminating a range of doses of cocaine (2–10 mg/kg) from saline (Colpaert et al., 1978; Witkin et al., 1991; Callahan et al., 1991, Fowler et al., 1993). Furthermore, the ED$_{50}$ for D-amphetamine substitution is highly similar between the present study (~0.28 mg/kg) and these previous studies. It is not clear whether the failure of D-amphetamine to substitute in one female, and the substantially higher ED$_{50}$ (0.78 mg/kg) obtained in another female represents an important sex difference. In numerous previous studies, however, across a range of cocaine training doses and a range of species (although predominantly males), D-amphetamine appears to have fully substituted for cocaine in all animals tested (in addition to the rat studies, de la Garza and Johanson, 1983, de la Garza and Johanson, 1986; Johanson and Barrett, 1993; Jarbe, 1993). Thus, it is possible that this slight difference in D-amphetamine substitution indicates that for some female rats, the cocaine discriminative stimulus was slightly different than it was for males.

The general failure of opioids to substitute for cocaine in the present study also agrees with previous studies in male animals. For example, the µ agonist morphine did not substitute fully for cocaine in either sex in this study, and previous studies in male animals trained to discriminate cocaine from saline showed that µ agonists such as fentanyl, morphine, buprenorphine and DAMGO did not substitute fully for cocaine (Dykstra et al., 1992; Spealman and Bergman, 1992; Ukai et al., 1995; Broadbent et al., 1995). Additionally, the nonpeptidic δ agonist BW373U86 did not fully substitute for cocaine in the present or in previous studies (Spealman and Bergman, 1994; Broadbent et al., 1995; Negus et al., 1995). In contrast, there were sex differences in substitution of the κ agonist U69,593: 2 of 4 male rats (but 0 of 5 females) responded on the cocaine-appropriate lever at the intermediate dose of U69,593. Again, it is not clear whether this result represents a noteworthy sex difference. Spealman and Bergman

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<th>Table 2</th>
<th>Effect of cocaine on locomotor activity in female and male rats, as percent of saline control levels</th>
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<tr>
<td>Dose cocaine</td>
<td>Cocaine-discriminating$^a$</td>
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<td></td>
<td>Female</td>
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<tr>
<td>1.0 mg/kg</td>
<td>124%</td>
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<td>3.0 mg/kg</td>
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<td>10.0 mg/kg</td>
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$^a$ Cocaine-discriminating rats were tested with all cocaine doses (and saline) on separate days, in random dose order (different order each rat; N = 6/dose).

$^b$ Cocaine-naive rats were tested with only 1 cocaine dose (or saline) (N = 4 rats/dose). For all rats, injections were i.p., 15 min pre-session. Sessions were 60 min long.
cocaine injections (either during the discrimination procedure, or the locomotor procedure, or both). Cocaine- 

nated rats had become sensitized due to repeated locomotor activating effects of psychostimulants have however, female drug discrimination rats also showed been demonstrated previously for the acute locomotor greater cocaine-induced locomotor activation than co-

motive effects in cocaine discrimination, females were much been studied, which showed that the agonists dynorphin A-(1-13) and U50,488 did not substitute for cocaine in rats trained to discriminate 10 mg/kg cocaine from saline (Broadbent et al., 1995; Ukai et al., 1995). In this case, again it may be concluded that the cocaine discriminative stimulus was slightly different for females than it was for some males. In general, despite the fact that previous studies indicate sex differences in antinociceptive (Baamonde et al., 1989; Kepler et al., 1991) and discriminative (Craft and Stratmann, 1996) effects of opioids, there were few sex differences in opioid effects in the present study. 

The cocaine discriminative stimulus was antagonized by the typical antipsychotic fluphenazine. This result agrees with previous studies indicating that both D1 and D2 receptor antagonists can block the discriminative stimulus effects of cocaine (Kleven et al., 1990; Callahan et al., 1991; Spealman et al., 1991; Johanson and Barrett, 1993). The fact that there were no significant sex differences in antagonism of the cocaine cue suggests that cocaine's discriminative stimulus effects are mediated by the same receptor types in both sexes. However, because fluphenazine is a non-selective phenothiazine that binds to both D1 and D2 receptors (Meltzer et al., 1989) as well as to various 5-HT receptors (Meltzer et al., 1989; Canton et al., 1994), it cannot be concluded that there are absolutely no sex differences in cocaine's mechanism of action. For example, it is possible that cocaine's effects are somewhat more serotonergic in females than in males, but this might not be evident using a non-selective antagonist such as fluphenazine. Examination of more receptor-selective antagonists would further elucidate whether there are any sex differences in the mechanism of cocaine's discriminative stimulus effects. 

Although female and male rats exhibited few differences in cocaine discrimination, females were much more sensitive to cocaine than males on a test of spontaneous locomotor activity. Such sex differences in locomotor activating effects of psychostimulants have been demonstrated previously for the acute locomotor activating effects of cocaine (Heyser et al., 1994) and D-amphetamine (Beatty and Holzer, 1978; Becker et al., 1982; Forgic and Stewart, 1994). In the present study, however, female drug discrimination rats also showed greater cocaine-induced locomotor activation than cocaine-naive females, suggesting that the drug discrimination rats had become sensitized due to repeated cocaine injections (either during the discrimination procedure, or the locomotor procedure, or both). Cocaine-induced sensitization has been demonstrated previously in both female and male rats, and females tend to sensitize more robustly than males do (Camp and Robinson, 1988; Ujike et al., 1995). Interestingly, despite their apparent sensitization to cocaine's locomotor effects, female drug discrimination rats did not develop sensitization to cocaine's discriminative or response rate-altering effects. That is, the ED50 for cocaine discrimination readetermined after all substitution and locomotor tests was approximately the same as the initial ED50. Additionally, in the drug discrimination task, females showed only slightly greater rates of responding than males after cocaine administration, and this marginal sex difference did not become any greater over the course of the study. These results suggest that there are different neurobiological mechanisms underlying spontaneous locomotor vs. discriminative effects of cocaine, and that even different types of locomotor activity (spontaneous vs. operant) are differentially sensitive to cocaine's activating effects. 

To determine whether sex differences in cocaine's potency as a discriminative stimulus might exist at a higher, more conventional training dose, rats were retrained at the end of the present study to discriminate 10 mg/kg cocaine from saline. The ED50 values obtained under the 10 mg/kg training dose were approximately the same as those obtained under the 5.6 mg/kg training dose. This result agrees with a previous study in which different groups of male rats were trained to discriminate either 5 or 10 mg/kg cocaine from saline (Callahan et al., 1992), although significant differences in ED50 values have been demonstrated when cocaine training doses were more disparate (at least 0.5 log unit apart: Spealman and Bergman, 1994; Terry et al., 1994; Kantak et al., 1995). Thus, it may be concluded from the present results that there are no substantial sex differences in the potency of cocaine's discriminative stimulus effects in the rat, even at a higher training dose. 

It is possible that sex differences in cocaine's discriminative effects were not observed in the present study because of cocaine's effects on gonadal hormones. That is, cocaine is known to alter hormonal status (King et al., 1990, 1993; Mello et al., 1990, 1993), and it is possible that the regime of cocaine administration used was sufficiently disruptive such that female and male rats were no longer 'hormonally distinct'. Differences in adult reproductive hormonal status underlie at least some of the sex differences in locomotor effects of psychostimulants (Robinson et al., 1981, Forgic and Stewart, 1994). Thus, several female rats were examined for estrous cyclicity for a week during the beginning and end of the study; all of them showed at least 1 day of proestrus, estrus and diestrus during each week. Although it cannot be concluded from these results that hormonal cycles were absolutely 'normal' in these fe
males, it does indicate that they were not severely disrupted. In addition, the fact that there were significant sex differences in locomotor activating effects of cocaine suggests that sex differences in cocaine's behavioral effects may not be dependent on adult reproductive hormonal differences.

In conclusion, the present study indicates that there are few sex differences in discriminative stimulus effects of cocaine in the rat, despite the fact that significant sex differences in cocaine's locomotor activating effects were observed. Sex differences in cocaine discrimination also may not correlate well with sex differences in cocaine self-administration, as female rats have been shown to self-administer cocaine to higher breaking points than males do (Roberts et al., 1989). Thus, it may be concluded from the limited animal data currently available that sex differences in cocaine self-administration may be related to sex differences in locomotor activating effects of cocaine, but probably not to sex differences in the ability to discriminate cocaine. To date, only a few human studies have been conducted to specifically examine gender differences in drug discrimination. However, those studies generally corroborate the present results: two studies reported no gender differences in acquisition of a D-amphetamine discrimination (or in subjective effects), particularly when gender differences in body weight were accounted for (Chait et al., 1989, Chait, 1993). In addition, there were no differences between men and women in trials to acquire a nicotine discrimination, or in the ED50 for nicotine discrimination (Perkins et al., 1994). However, there were gender differences in the correlation between nicotine-appropriate responding and subjective effects (Perkins et al., 1994), as well as in the effects of pre-loading on subsequent smoking behavior (Perkins et al., 1992), and several other variables related to drug-taking behavior (Perkins et al., 1995). Thus, even in humans, gender differences (or lack thereof) in the drug discrimination procedure may not be predictive of (or explain) gender differences in drug effects or drug-taking behavior. It is important to emphasize, however, that very few studies have specifically examined gender as a subject variable. Further research will clarify whether gender differences in self-administration, discrimination and other drug effects are consistent across different classes and doses of abused drugs, and ultimately, whether there is any significant biological basis for gender differences in drug use and addiction.

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