

# Limited Sex Differences in Response to “Binge” Smoked Cocaine Use in Humans

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*The subjective and physiological effects of repeated smoked cocaine self-administration were compared in 11 men and 9 women. Twice a day, on 2 consecutive days, participants smoked up to six 50-mg doses of cocaine base, at 14 min intervals. Men and women self-administered a similar number of cocaine doses (21.7 and 21.6, respectively). The most striking sex difference was that women had higher cocaine plasma concentrations than men (632.7 ng/ml vs. 376.7 mg/ml) after the sixth cocaine dose of the first session. After the first cocaine dose, women reported that they would spend significantly less for the dose than men (\$1.58 vs.*

*\$3.15). Although cocaine produced similar effects in men and women 4 min after each dose, 15 min after the last dose of the session, heart rate and blood pressure remained elevated in women, but ratings of “I want cocaine” were lower in women as compared to men. Thus, smoking cocaine produced similar acute subjective effects in men and women, but prolonged cardiovascular effects and higher cocaine plasma concentrations in women.*

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Although women make up as much as one-third of the cocaine-abusing population (USDHHS 1993), relatively few preclinical or clinical studies have investigated sex differences in response to cocaine administration. Among the laboratory animal literature, some studies have found no or few cocaine-related sex differences (e.g., Foltin and Schuster 1982; van Haaren and Hughes 1990; Haney et al. 1995; Craft and Stratmann 1996). Although other studies have documented sex differences, the question of whether female rodents are more or less sensitive to the effects of cocaine has not been resolved. For example, cocaine administration increased locomo-

tor activity more in intact female rats (van Haaren and Meyer 1991; Haney et al. 1994) than in either ovariectomized female rats or male rats (either intact or castrated); whereas, cocaine increased locomotor activity less in female mice than in male mice (Morse et al. 1993). However, Morishima et al. (1993) showed that male rats and ovariectomized female rats were more sensitive to the toxic effects of cocaine than intact females. With respect to cocaine self-administration, no sex, hormonal, or estrous cycle differences have been observed under a fixed ratio one schedule of intravenous cocaine self-administration (Dalton et al. 1986; Roberts et al. 1987, 1989; Haney et al. 1995). However, the dopamine antagonist haloperidol increased cocaine self-administration more in female than in male rats (Dalton et al. 1986). In addition, the effect of haloperidol on cocaine self-administration varied across the estrous cycle and was reduced in ovariectomized females (Roberts et al. 1987). Furthermore, when a progressive-ratio schedule of reinforcement was employed, sex differences in cocaine self-administration were observed; female rats had higher breakpoints than male rats, particularly during the estrus phase (Roberts et al. 1989).

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Taken together, these preclinical findings suggest that there are sex differences in response to cocaine on some behaviors, which may vary as a function of gonadal hormone levels.

Several clinical studies have investigated whether female and male cocaine abusers differ with respect to socioeconomic status, prevalence of psychiatric disorders, treatment retention and relapse, and abnormalities in cerebral perfusion (e.g., Griffin et al. 1989; Kosten et al. 1993; Levin et al. 1994; Lundy et al. 1995; Dudish and Hatsukami 1996). However, to our knowledge, only four controlled studies have evaluated the direct effects of cocaine administration in women (Dudish et al. 1996; Kosten et al. 1996; Lukas et al. 1996; Haney et al. 1998). Two of these studies compared the effects of acute doses of intranasal cocaine in men and women (Kosten et al. 1996; Lukas et al. 1996). Following a single intranasal dose of approximately 2 mg/kg cocaine, no differences in cardiovascular effects or ratings of "high" were observed between males and females (Kosten et al. 1996). Similarly, Lukas et al. (1996) found no difference in cardiovascular response in males and females following a single dose of 0.9 mg/kg intranasal cocaine, but men had higher cocaine plasma concentrations than women, and men reported more rapid and intense subjective effects than women. In contrast, in a recent study by Haney et al. (1998), although sex differences were not the focus of the study, there was a trend for women to be less sensitive to the cardiovascular and subjective effects of multiple doses of intravenous cocaine than men. Although Dudish et al. (1996) investigated repeated doses of smoked cocaine in females and found that females self-administered smoked cocaine in a dose-related manner with no untoward cardiovascular or subjective effects, they did not test men using the identical procedure. Thus, there are currently no laboratory data directly comparing the effects of repeated doses of smoked cocaine in men and women, obtained under identical laboratory conditions.

The purpose of the present study was to determine if sex differences exist in response to repeated doses of smoked cocaine base. This was accomplished by combining portions of data previously reported on the effects of cocaine in 11 male (Ward et al. 1997a; Haney et al. unpublished data) and nine female (Evans et al. 1998) cocaine abusers. Although these studies differed with respect to the duration of the study, the total number of days of cocaine self-administration, and other factors (see below for details), in each of these studies, participants self-administered smoked cocaine six times per session, two sessions daily, for 2 consecutive days under identical laboratory conditions. Given that the dosing procedures, questionnaires, and physiological monitoring were *identical* across these three studies during 2 days of cocaine self-administration sessions, combining across these datasets provides a sufficient

sample size to address the new question about potential sex differences in response to smoked cocaine.

## MATERIALS AND METHODS

### Subjects

Eleven male research volunteers (seven African American, three Hispanic, and one Asian), 26 to 41 years of age (mean = 35) and nine female research volunteers (seven African American and two Caucasian) 34 to 43 years of age (mean = 39), with current histories of smoking cocaine were solicited through newspaper advertisement in New York, NY. Men reported currently spending \$50 to \$250 (mean = \$153) per week on cocaine and using cocaine an average of 4 days each week. Similarly, women reported currently spending \$30 to \$210 per week on cocaine (mean = \$129) and using cocaine an average of 4 days each week. Eight of the men smoked cigarettes (mean of 19 cigarettes/day) and seven of the women smoked cigarettes (mean of 14 cigarettes/day). Men weighed more than women ( $77.7 \pm 5.0$  kg vs.  $61.4 \pm 3.2$  kg). Men and women had similar education levels (mean of 12.0 years for men and 12.4 years for women). All volunteers were medically and psychiatrically healthy based upon a physical examination, electrocardiogram, cardiac stress test, chest X-ray, complete blood chemistries (including pseudocholinesterase levels), urinalyses, and a structured psychiatric interview. Before study participation, levels of plasma pseudocholinesterase, which is responsible for the debenzoylation of cocaine (Inaba 1989), were determined. The levels were within the normal range for both men and women ( $5.0 \pm 0.6$  and  $4.1 \pm 0.3$  mU/ml, respectively) and did not vary between the sexes. None was receiving psychiatric treatment or seeking treatment for their drug use. None of the female participants was using hormonal contraceptives or any other prescription medication. Also, women were not pregnant (based on blood pregnancy tests) or nursing and had not had an abortion or been pregnant within the previous 6 months. Each participant signed a consent form, approved by the Institutional Review Boards of The College of Physicians and Surgeons of Columbia University and The New York State Psychiatric Institute. The consent form described the study, outlined possible risks, and indicated that cocaine would be administered, possibly on a daily basis. Participants were paid for their participation in multiple weekly payments not to exceed a value of \$300 each week; women were paid with a combination of cash and gift certificates.

### Design and Experimental Procedures

Women were typically admitted on a Friday or a Monday to the NIH-funded Irving Center for Clinical Re-

search in the Presbyterian Hospital and resided there for four or five nights (Evans et al. 1998). Men were admitted on a Friday and resided on the unit for 14 (Ward et al. 1997a;  $n = 7$ ) to 20 days (Haney et al. unpublished data;  $n = 4$ ). All participants had access to television, radio, and video-taped movies while on the Clinical Research Center, but were not permitted to leave the unit unless accompanied by a staff member. Participants who smoked tobacco cigarettes were allowed to smoke throughout their inpatient stay. However, smoking was not allowed during experimental sessions, which lasted approximately 2.5 hours each. The nine women participated in 2 consecutive days of cocaine self-administration sessions with two sessions each day, and this inpatient phase was followed by a 2-week out-patient phase (see Evans et al. 1998 for details). Seven of the men participated in both 2 and 3 consecutive days of cocaine self-administration sessions, with two sessions each day (see Ward et al. 1997a). Data from the first 2 days of sessions were used in the present analyses. The other four men resided on the residential unit for 20 days. During the 1st week, participants had 3 consecutive days of cocaine self-administration sessions, with two sessions each day followed by 2 weeks when no cocaine was available. During this time, the effects of d-fenfluramine on plasma levels of cortisol and prolactin were determined (Haney et al. unpublished data). Again, only data from the first 2 days of sessions were used in the present analyses. Given that the dosing procedures, questionnaires, and physiological monitoring (with the exception of blood collection) were identical across the three studies during the first 2 days of cocaine self-administration sessions (see Ward et al. 1997a for details), we utilized this opportunity to make direct comparisons between men and women in response to smoked cocaine self-administration. Because other aspects of these studies were different (e.g., duration of stay, total number of days of cocaine self-administration, challenges with fenfluramine, etc.), the only data used for the present analyses were from the first 2 days of smoked cocaine self-administration, which were identical across all three of these studies.

**Experimental Sessions.** Each day there were two experimental sessions, one at 1200 h and another at 1600 h. During experimental sessions, each participant was seated in a comfortable lounge chair in front of a computer monitor on which subjective-effects questions were displayed. A mouse was used for completion of the subjective-effects questionnaire. An 18-gauge catheter (Quik-Cath®, Travenol Laboratories, Deerfield, IL) was inserted into a subcutaneous vein in one arm for blood collection. The intravenous line was kept patent by a physiological saline solution drip at a rate of 2 cc/min. An electrocardiogram was continuously monitored via chest electrodes (MAC PC®, Marquette Elec-

tronics, Milwaukee, WI), and heart rate and blood pressure were recorded every 2 minutes (Sentry II - Model 6100 automated vital signs monitor, NBS Medical, Costa Mesa, CA) beginning 30 min before drug administration. A Macintosh computer located in an adjacent room was used for automated data collection.

Each cocaine self-administration session began with 30 min of baseline vital signs and participants completing the baseline subjective-effects questionnaire at -30 min and -10 min. During each cocaine self-administration session, participants had the opportunity to self-administer either 50 mg cocaine base or take nothing six times/session at 14-min intervals, with the first dose given at time 0. Choice trials were signaled by the appearance in outline form of two squares ( $3 \times 3$  cm) on the computer monitor. Participants selected an option by moving the mouse (illuminating the square associated with that position) to the left, indicating a choice to take cocaine, or the right, indicating a choice to take nothing. Participants were then required to press the space bar or Enter key 200 times, as a confirmatory component of the choice procedure. Once the response requirement was completed, the message "Left (or Right) Option chosen" appeared at the bottom of the screen. The research nurse then entered the session room and presented the participant with 50 mg of cocaine base in a glass pipe ("stem") fitted with smoking screens. Participants were instructed to take one large inhalation and to hold the inhalation as long as they normally would outside of the laboratory. Pyrolysis of the cocaine base was accomplished by the nurse holding the flame from a pipe lighter on the cocaine.

During the session, the subjective-effects questionnaire was repeated 4 min after administration of each cocaine dose (even if a dose was not given), as well as 15 min after the last cocaine dose. Cocaine was not given on any trial that any cardiovascular measure was above our criteria for safe drug administration (heart rate  $> 130$ , diastolic pressure  $> 100$ , systolic pressure  $> 165$ ). During all sessions, participants were continuously monitored via a one-way mirror by research nurses located in the adjacent room, and participants could communicate with nurses via an intercom system.

**Subjective-Effects Questionnaires.** A computerized questionnaire was completed repeatedly during each session: 30 min and 10 min before the first cocaine dose, 4 min after each cocaine dose, and 15 min after the last cocaine dose. The questionnaire consisted of a series of 100-mm visual analog scales (VAS) labeled "Not at all" (0 mm) at one end and "Extremely" (100 mm) at the other end. Eighteen of these VAS were labeled "Stimulated," "High," "Anxious," "Sedated," "Depressed," "Hungry," "Friendly," "Miserable," "On edge," "Alert," "Tired," "Talkative," "Self-confident," "Social," "Irritable," "Confused," "Good drug effect," and "Bad drug

effect." Four VAS were used to operationalize drug craving and were labeled "I want . . ." " . . . Cocaine," " . . . Heroin," " . . . Ethanol," and " . . . Nicotine." Three VAS were related specifically to the cocaine dose the participant had just received and were labeled "The choice was of high quality," "The choice was potent," and "I liked the choice." A final question asked the participants "How much would you pay for the dose you just received?" with a range of \$0 to \$25.

Each evening during the inpatient phase and for a 2-week outpatient phase (Evans et al. 1998), female participants completed a Daily Ratings Form (Endicott et al. 1986). This questionnaire was used to assess possible changes in mood across the menstrual cycle and to document the onset and duration of menstruation, which would then be used to approximate the phase of the menstrual cycle during which women participated in the 2 days of cocaine self-administration and to determine if any of them experienced substantial mood changes premenstrually (late luteal phase). The form consists of 21 items describing problems with mood, behavior, and physical symptoms. Three additional items determined if any of these problems interfered with work or school, social activities, or interpersonal relationships. Before going to bed, women rated the severity of each of these symptoms on a 6-point scale, from 1 ("not at all") to 6 ("extreme"). The measure used to determine the level of symptoms each day was the mean score of all 24 items.

Based on the prospective information obtained from the Daily Ratings Forms, women were at various phases of their menstrual cycle during the 2-day period of cocaine self-administration. It was estimated that two women were in the ovulatory phase, two were in the midluteal phase, three were in the late luteal phase, and two were in the menstrual phase. However, this was only an approximation, because ovulation was not determined, and hormone levels of estradiol and progesterone were not measured.

**Drug.** Cocaine base, derived from cocaine hydrochloride (provided by The National Institute on Drug Abuse) as described in Foltin et al. (1990), was prepared by the Presbyterian Hospital Manufacturing Pharmacy.

**Cocaine analysis.** Venous blood samples (approximately 6 ml) for cocaine were drawn from an indwelling catheter into tubes containing potassium oxalate and sodium fluoride. Samples were immediately mixed and placed on ice until they could be centrifuged. They were centrifuged within 30 min of collection, yielding approximately 3 ml of plasma, and stored frozen until the time of analysis. Because blood samples were not collected in all participants, and the number and timing of samples varied across the studies [e.g., in the unpublished study by Haney et al., blood samples for cocaine were obtained only at baseline (before the first cocaine

dose), 4 min after the first dose, and 4 min after the sixth dose], only available blood samples collected on the first session of the first self-administration day at the same time points for all available participants were analyzed. Thus, cocaine samples drawn before the first cocaine dose, 4 min after the first dose, and 4 min after the sixth dose were compared for six men and six women.

Cocaine blood concentrations were determined by Thomas Cooper at the Nathan Kline Institute for Psychiatric Research (Orangeburg, NY). Cocaine and benzoylecgonine were analyzed by capillary gas chromatograph-mass spectrometry using deuterated internal standards, positive chemical ionization, and simultaneous ion monitoring. Intra- and interassay coefficients of variation are less than 6% for all compounds.

**Data Analysis.** Mean heart rate, systolic pressure, and diastolic pressure, averaged across 8 min, were collected beginning 30 and 10 min before the first cocaine dose, 2 min after each cocaine dose, and 15 min after the last cocaine dose, for a total of nine measurements within a session. Similarly, each VAS was collected nine times within a session. Each cardiovascular measure and each VAS item was analyzed separately. The repeated-dose effects of cocaine within a session were examined using four-factor repeated-measures analyses of variance (ANOVA) with sex (male vs. female) as the first factor, day (1st day vs. 2nd day) as the second factor, self-administration session as the third factor (1200 h session vs. 1600 h session) and time as the fourth factor (nine times for both cardiovascular and subjective-effects measures). Similarly, for both cardiovascular and subjective-effects measures, separate analyses were conducted to determine: (1) baseline differences before cocaine administration each session; (2) acute differences following the first cocaine dose each session; and (3) differences following the sixth cocaine dose each session. The area under the curve (AUC) from time zero to the end of each laboratory session, determined using Simpson's Rule (Tallarida and Murray 1981), was also analyzed for each of the cardiovascular measures, expressed as a change from the initial baseline. Each of these analyses used a three-factor repeated-measures ANOVA with sex as the first factor, day as the second factor, and self-administration session as the third factor. Last, cocaine and benzoylecgonine plasma concentrations, using the first self-administration session that blood was collected, were analyzed separately using a two-factor repeated-measures ANOVA with sex and time as the two factors.

A secondary set of analyses on selected measures was conducted to determine further whether differences in cocaine plasma concentrations between men and women were related to differences in cardiovascular and subjective changes in response to cocaine. For

this set of analyses, only the cardiovascular and subjective measures from the first self-administration session that blood was collected from the six men and six women were analyzed. Systolic pressure, diastolic pressure, heart rate, and rating of "Stimulated," "Self-confident," "High," "Alert," "Good drug effect," "Bad drug effect," and "I want cocaine" were analyzed separately using a two-factor repeated-measures ANOVA with sex and time as the two factors.

For all analyses, results were considered statistically significant if  $p < .05$ . Because the effects of smoked cocaine have been described in the earlier reports (see Ward et al. 1997a; Evans et al. 1998) that provided portions of the data for this new analysis, the results specifically pertaining to significant effects of sex will be emphasized.

## Results

**Baseline Differences.** The only baseline sex difference was that men had significantly higher systolic pressure before cocaine administration than women ( $p < .0066$ ). However, baseline systolic pressure ( $p < .0001$ ), diastolic pressure ( $p < .0001$ ), and heart rate ( $p < .0001$ ) were all significantly increased in both men and women for the 1600-h session as compared to the 1200-h session. Baseline heart rate was also significantly increased on the 2nd day as compared to the 1st day ( $p < .0226$ ). With respect to subjective effects, baseline ratings of "Anxious" ( $p < .05$ ) were significantly higher for the 1200-h session as compared to the 1600-h session; whereas, baseline ratings of "I want cocaine" were increased more for the 1600-h session than the 1200-h session ( $p < .0453$ ), regardless of sex.

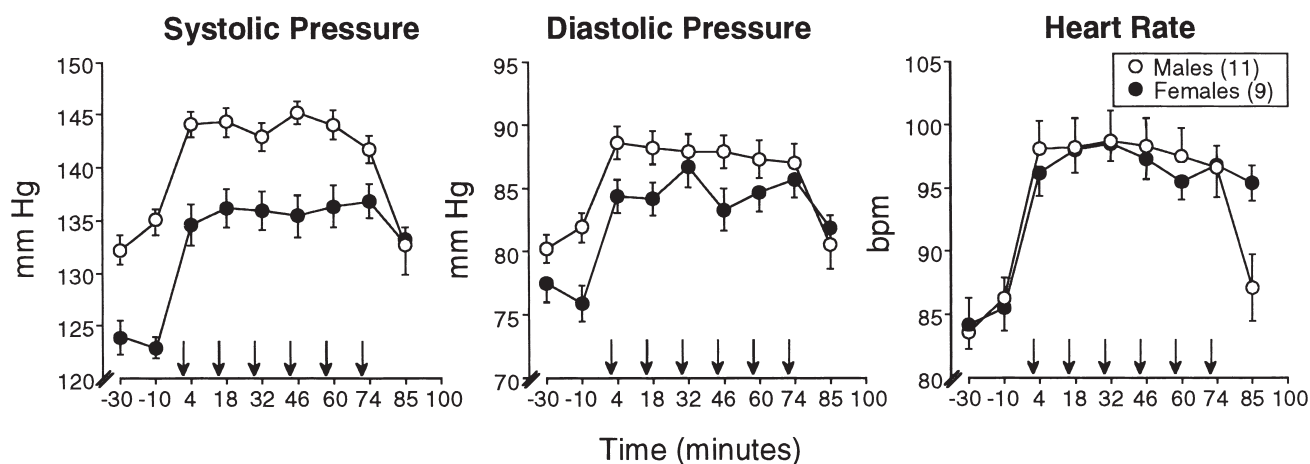
**Cocaine Self-Administration.** Cocaine was self-administered on 91 and 90% of the choice trials for men and women, respectively (data not shown). Cocaine doses were withheld slightly more often for men (<5% of the choice trials) than for women (<3% of the choice trials), because vital signs were elevated above criteria for cocaine administration. In contrast, women refused a slightly higher percentage of cocaine doses than men (7 and 5%, respectively). However, overall, men and women received a similar number (21.7 and 21.6 respectively, out of 24) of cocaine doses.

## Time Course Effects of Cocaine Within a Session.

Figure 1 shows the effects of repeated doses of cocaine within a session on cardiovascular measures as a function of time and sex. All cardiovascular measures increased following the first dose of cocaine, with no further increases following subsequent cocaine doses within a session. For each of these measures, there was a significant Time  $\times$  Sex effect (systolic pressure:  $p < .0112$ ; diastolic pressure:  $p < .0239$ ; heart rate:  $p < .023$ ). Although men had higher systolic pressure and diastolic pressure than women, both systolic pressure and diastolic pressure remained elevated 15 min after the last dose of the session in women, but not in men. Even more striking was heart rate; although heart rate returned to baseline levels for men, heart rate was 10 bpm higher than baseline for women.

To determine whether the cardiovascular differences between men and women were related to baseline differences, AUC analyses from time zero to the end of each laboratory session were conducted for each of the cardiovascular measures, expressed as a change from the initial baseline. Based on AUC analyses (data not

## Cardiovascular Effects within Self-Administration Sessions



**Figure 1.** Time course of cardiovascular measures averaged within self-administration sessions as a function of sex. Datapoints at each time show means across all four sessions for 11 men and 9 women, respectively. Arrows indicate each cocaine dosing within a session and error bars represent  $\pm 1$  SEM.

shown), the only cardiovascular measure that showed an interaction with sex was heart rate, which was significantly lower in women than in men during the 1600-h session compared to the 1200-h session (Session  $\times$  Sex;  $p < .0373$ ).

Overall, smoked cocaine significantly increased all but three subjective-effects measures within a session including "Alert" ( $p < .0011$ ), "Self-confident" ( $p < .002$ ), "High" ( $p < .0001$ ), "Good drug effect" ( $p < .0001$ ), and "Stimulated" ( $p < .0001$ ). The three subjective-effects measures that were not altered by cocaine were "Irritable," "Tired," and "I want heroin." However, there were relatively few subjective differences in response to smoked cocaine during a session between men and women. Figure 2 shows the effects of repeated doses of cocaine within a session on selected subjective-effects measures that did differ as a function of time and sex. Although ratings of "I want cocaine" were similar for men and women at baseline, within a session, these ratings decreased for women and increased for men (Day  $\times$  Time  $\times$  Sex;  $p < .05$ ). In contrast, ratings of "I want nicotine" significantly increased throughout the session for women, but remained stable for men (Time  $\times$  Sex;  $p < .0001$ ), even though a similar number of men and women smoked cigarettes. Similar effects were also observed for ratings of "I want alcohol" (Time  $\times$  Sex;  $p < .0041$ ; data not shown). Lastly, ratings of "Bad drug effect" increased over the course of a session for women, but not for men (Session  $\times$  Sex;  $p < .0428$ ).

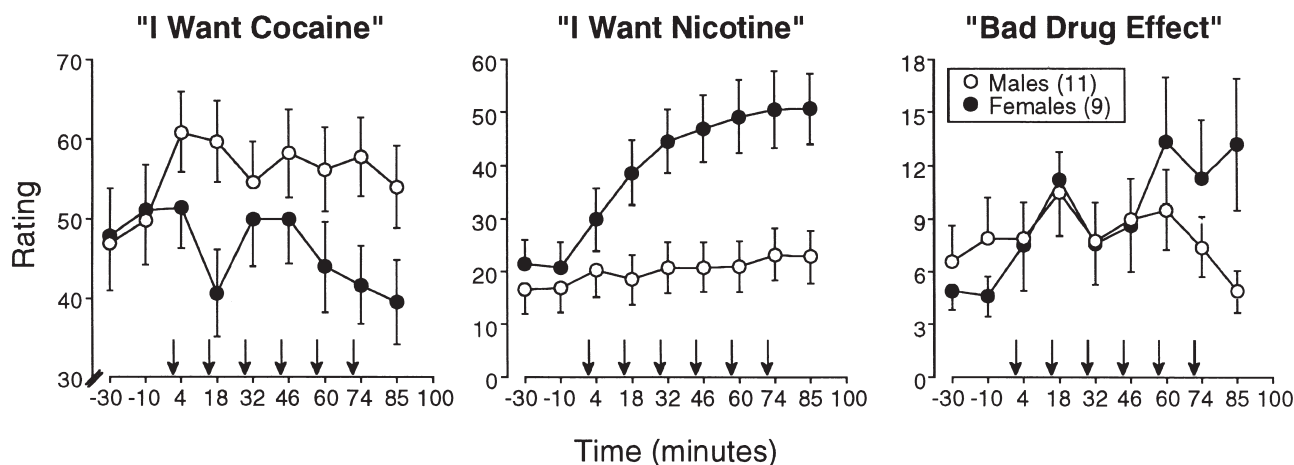
**Plasma Concentrations.** Table 1 compares venous cocaine and benzoylecgonine plasma concentrations in males ( $n = 6$ ) and females ( $n = 6$ ) during the first cocaine self-administration session. Women had higher

cocaine plasma concentrations than men ( $p < .0001$ ), and there was a significant Time  $\times$  Sex interaction ( $p < .0077$ ), so that at 74 min, 4 min after the last cocaine dose, cocaine plasma concentrations for women were 632.7 ng/ml and only 376.7 ng/ml for men. There were no differences between men and women with respect to benzoylecgonine plasma concentrations during the cocaine self-administration session.

Despite the higher cocaine plasma concentrations in women after the last cocaine dose, based on a secondary set of analyses comparing selected cardiovascular and subjective effects between the six males and six females for whom we had corresponding blood samples, there were no differences between these men and women on systolic pressure, diastolic pressure, heart rate, and rating of "Stimulated," "Self-confident," "High," "Alert," "Good drug effect," "Bad drug effect," and "I want cocaine."

**First Dose Effects.** Figure 3 shows the effects of the first dose of cocaine on selected cardiovascular and subjective effects as a function of sex, session, and day. The first dose of cocaine increased systolic pressure more in men than in women, as indicated by a significant sex difference ( $p < .013$ ), although this was accounted for by the higher baseline systolic pressure in men. In contrast, the heart rate increases observed following the first dose of cocaine were similar across sex, session, and day. There were also sex differences regarding how much participants were willing to pay for the first cocaine dose and how anxious they were following the first dose (Figure 3, lower panels). Women reported that they would spend significantly less for the first cocaine dose of a session than men (\$1.58 vs. \$3.15;  $p < .05$ ).

### Subjective Effects within Self-Administration Sessions



**Figure 2.** Time course of selected subjective-effects measures averaged across all self-administration sessions as a function of sex. For details, see Figure 1.

**Table 1.** Comparison of Cocaine and Benzoyllecgonine Plasma Concentrations in Men and Women<sup>a</sup>

Time (min) <sup>b</sup>	Cocaine Concentrations (ng/ml)		Benzoyllecgonine Concentrations (ng/ml)	
	Men	Women	Men	Women
Baseline	3.8 (± 2.6)	4.8 (± 2.9)	1.2 (± 1.2)	3.5 (± 2.6)
4 min	106.3 (± 30.5)	157.5 (± 37.6)	8.7 (± 1.2)	28.7 (± 9.8)
74 min	376.7 (± 61.1)	632.7 (± 84.2)	531.0 (± 109.9)	561.0 (± 60.4)

<sup>a</sup>Values represent the mean and ± 1 SEM for six men and six women, respectively.

<sup>b</sup>Baseline is 5–10 min before the first cocaine dose, 4 min is 4 min after the first cocaine dose, and 74 min is 4 min after the last cocaine dose of the first session.

.041). Although there were no baseline differences with respect to ratings of "Anxious," men tended to be more anxious than women following the first cocaine dose of a session ( $p < .06$ ). In addition, ratings of "Good drug effect" showed a significant Day  $\times$  Sex effect ( $p < .0196$ ; data not shown) in that women liked the first cocaine dose more on the first day as compared to the second day (mean of 61.8 vs. 50.3); whereas, the opposite was true for the men, who indicated they liked that dose less on the first day as compared to the second day (mean of 45.2 vs. 59.3). Last, several subjective measures showed significant Day  $\times$  Session  $\times$  Sex effects; ratings of "I liked the choice" ( $p < .0151$ ), "The choice was potent" ( $p < .0297$ ) and "Self-confident" ( $p < .05$ ) were all significantly lower following the first cocaine dose of the second session on the second day for women, but not for men (data not shown). Other than these few measures, men and women did not differ in response to the first cocaine dose of each session.

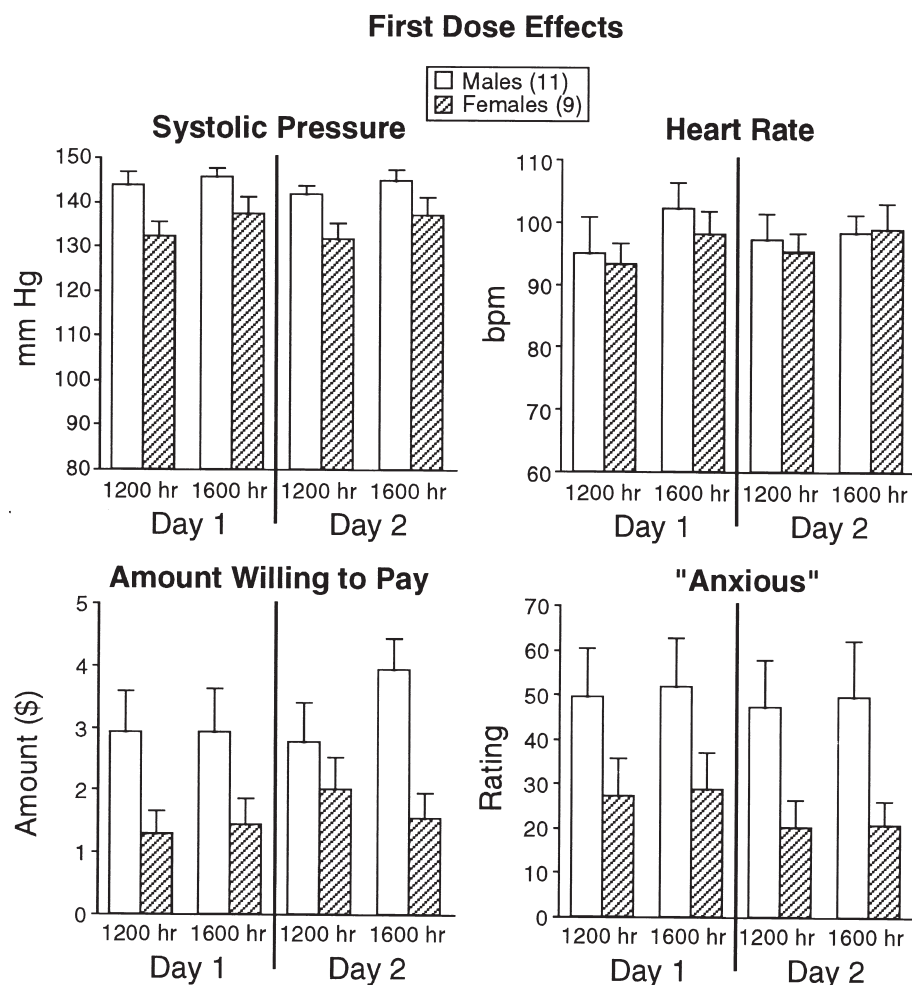
**Last Dose Effects.** Although cocaine plasma concentrations were significantly higher in women after the last cocaine dose as compared to men, only three other measures showed any sex differences. Similar to the time course effects, ratings of both "Bad drug effect" (Day  $\times$  Sex;  $p < .05$ ) and "I want alcohol" (Day  $\times$  Sex;  $p < .0446$ ) were significantly higher in women than in men. In contrast, men reported higher ratings of "Confused" than women (Day  $\times$  Sex;  $p < .0313$ ) following the last cocaine dose of a session.

## DISCUSSION

To our knowledge, this is the first study to compare directly the effects of repeated smoked cocaine use in men and women under controlled laboratory conditions. Self-administration sessions occurred twice daily on 2 consecutive days, during which participants could smoke up to six doses of 50 mg cocaine base each session, with doses spaced 14 min apart. There was no difference between men and women in the number of co-

caine doses self-administered. Furthermore, for both men and women, all cardiovascular measures increased above baseline levels following the first dose of cocaine, with no further increases following subsequent cocaine doses within a session. Similarly, smoked cocaine significantly increased all but three subjective-effects measures in both men and women. The increases in cardiovascular and subjective effects observed following repeated doses of smoked cocaine in the present study are consistent with the spectrum of cocaine effects in humans previously reported by others (Kumor et al. 1989; Foltin and Fischman 1991; Hatsukami et al. 1994; Ward et al. 1997a; Evans et al. 1998).

The most striking sex difference in the present study was that women had higher cocaine plasma concentrations than men. Although cocaine plasma concentrations 4 min after the first cocaine dose were similar in men and women, they were significantly higher in women after the last cocaine dose. In contrast, benzoyllecgonine plasma concentrations did not differ between men and women. It is possible that women were not metabolizing cocaine as efficiently as men, and had we continued to measure plasma concentrations, benzoyllecgonine plasma concentrations may have continued to rise in women as compared to men. To our knowledge, only one other study, conducted in men, measured cocaine and benzoyllecgonine plasma concentrations after repeated doses of cocaine (Isenschmid et al. 1992). They found that after the last cocaine dose, cocaine and benzoyllecgonine plasma concentrations were similar to each other, which was also observed in the present study. The differences between men and women with respect to cocaine plasma concentrations are not in complete agreement with previous studies that have shown either no difference (Kosten et al. 1996), or higher cocaine plasma concentrations (Lukas et al. 1996) in men compared to women following acute doses of intranasal cocaine. Similarly, although Dudish et al. (1996) did not directly compare the effects of smoked cocaine in men and women, they reported that the cocaine plasma concentrations in women were similar to those of men following a 0.4 mg/kg dose of smoked cocaine (101 ng/ml



**Figure 3.** Mean cardiovascular and selected VAS subjective-effects measures averaged after the first cocaine dose as a function of session, day and sex. Bars represent the mean + 1 SEM.

vs. 161 ng/ml, respectively). The higher cocaine plasma concentrations in women observed in the present study are most likely attributable to women receiving effectively higher doses of cocaine than men, because the doses administered were not based on body weight, and women weighed substantially less than men ( $61.4 \pm 3.2$  kg vs.  $77.7 \pm 5.0$  kg, respectively). If dosing had been based on body weight, then based on extrapolation, women would presumably have had lower cocaine plasma levels than men following the first dose. However, this still does not completely account for the large difference in cocaine concentrations between men and women following the sixth dose. Although the present study did not control for body weight, the procedure more closely reflects what happens in the natural environment; that is, women don't buy smaller vials of crack. Based on self-reports, women were using cocaine as frequently as men and spending a similar amount of money on cocaine. Moreover, during the study, women self-administered a similar number of cocaine doses as did men. At this time, it remains unclear whether the differences in cocaine plasma concentrations between men and women across studies are

related to the dosing procedure, the route of administration, acute versus repeated dosing, or such other factors as hormonal fluctuations.

Despite the fact that women had higher cocaine plasma concentrations than men, there were few cardiovascular differences between men and women following repeated smoked cocaine administration. Although men had higher baseline systolic pressure than women, the relative increase in all cardiovascular responses to cocaine relative to baseline were similar. However, in contrast to men, it did take longer for heart rate and blood pressure to return to baseline levels for women. Based on these findings, we might initially conclude that women are more sensitive to the cardiovascular effects of cocaine. However, there were no cardiovascular differences between men and women following the first cocaine dose, with the exception that systolic pressure was higher in men because of baseline differences, and these sex differences did not become apparent until after the last cocaine dose, when cocaine plasma concentrations were 60% higher in women. In fact, based on the AUC analyses, only heart rate showed an interaction with sex given that heart rate

was lower in women than in men during the second session within a day. If doses had been administered based on body weight, then perhaps the cardiovascular response would have been lower in women than in men, suggesting that women may actually be less sensitive to the cardiovascular effects of smoked cocaine. Similar conclusions were reached by Dudish et al. (1996) and Haney et al. (1998). In contrast, Lukas et al. (1996) concluded that women were more sensitive to the cardiovascular effects of cocaine, because although men had higher cocaine plasma concentrations than women, there were no sex differences in heart rate following a single dose of 0.9 mg/kg intranasal cocaine. However, inspection of the data and figures in that study shows a clear tendency for heart rate to be higher in men than in women; the failure to reach statistical significance may be a result of the small sample size and the relatively low cocaine dose. Last, another study (Kosten et al. 1996) found no differences between 23 males and 11 females on blood pressure or heart rate following a single dose of 2 mg/kg intranasal cocaine.

Overall, there were also relatively few subjective-effects differences between men and women following repeated smoked cocaine administration. These results are consistent with those reported by others (Kosten et al. 1996; Lukas et al. 1996; Haney et al. 1998) despite differences in route of administration, acute versus repeated dosing, or both. For example, women reported lower ratings of "Stimulated" and dose quality than men following repeated doses of intravenous cocaine (Haney et al. 1998). Taken together, the differences in cocaine's effects between men and women seem to be subtle.

In the present study, men and women differed on their reported desires for cocaine, nicotine, and alcohol. Within a session, cocaine significantly decreased ratings of "I want cocaine" in women, but not in men. In contrast, ratings of "I want nicotine" increased for women, but remained stable for men, although a similar number of men and women reported smoking cigarettes. Previous studies in male cocaine abusers have shown that the first dose of cocaine usually increases cocaine craving and that subsequent doses within a session do not alleviate this craving (Foltin and Fischman 1991; Ward et al. 1997a, b). It is unclear whether this reduction in cocaine craving with repeated dosing during a session is unique to females (Evans et al. 1998). Two previous studies that directly compared the effects of cocaine in males and females did not ask about cocaine craving or desire (Kosten et al. 1996; Lukas et al. 1996), and another study did not report any sex differences (Haney et al. 1998). Furthermore, in the study by Dudish et al. (1996); whereas, desire for cocaine increased as a function of dose in women, no data were presented regarding changes in desire for cocaine following repeated doses within a session.

One limitation of the present study is that women were not tested at the same phase of the menstrual cycle, and hormone concentrations were not measured (Evans et al. 1998). Based on the prospective information obtained from the Daily Ratings Forms, two women were in the ovulatory phase (11–14 days after the onset of menses), two were in the midluteal phase (6–10 days before the onset of menses), three were in the late luteal phase (5 days before the onset of menses), and two were in the menstrual phase during the 2-day period of cocaine self-administration. Similarly, Dudish et al. (1996), admitted and tested women at different phases of the menstrual cycle (because of difficulties with subject recruitment) and only four women had normal menstrual cycles. To date, only one study has compared the effects of cocaine in women at different phases of the menstrual cycle (Lukas et al. 1996). They found that women had higher cocaine plasma concentrations during the follicular phase as compared to the luteal phase following 0.9 mg/kg intranasal cocaine, although subjective and cardiovascular responses to cocaine did not differ as a function of menstrual cycle phase. Because several preclinical studies have shown sex differences in response to cocaine, and data suggest that these differences may be related to gonadal hormones (van Haaren and Meyer 1991; Morishima et al. 1993; Roberts et al. 1987, 1989), additional studies are needed to investigate pharmacodynamic and pharmacokinetic sex differences in response to cocaine more thoroughly. Moreover, these studies should test women at various phases of the menstrual cycle and examine the role of gonadal hormones.

The present study shows that, under controlled conditions in which 12 doses of cocaine are available each day for 2 days, women will self-administer the same number of smoked cocaine doses as men. Furthermore, although women achieve substantially higher cocaine plasma concentrations after repeated cocaine self-administration, in general, they do not seem to experience any greater subjective or cardiovascular response to cocaine. Taken together, these findings suggest that women may actually be less sensitive to the effects of smoked cocaine than men, although additional research focusing on sex differences in response to various routes of cocaine administration are clearly needed.

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