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Human Sex Differences in d-Amphetamine Self-Administration

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Abstract

Women and men may respond differently to the effects of stimulants such as amphetamine and cocaine.

Aim—In order to assess potential sex-differences in the reinforcing effects of *d*-amphetamine, a retrospective-analysis was conducted on data collected from three studies that employed similar *d*-amphetamine self-administration procedures and used identical subject-rated drug-effect measures.

Method—Data from ten women and fifteen men were included in the analysis. In all studies, participants sampled placebo, low (8 to 10 mg) or high (16 to 20 mg) dose oral *d*-amphetamine. Following sampling sessions, participants worked for capsules containing 12.5% of the previously sampled dose on a modified progressive-ratio schedule of reinforcement. We hypothesized that women and men would be differentially sensitive to the reinforcing effects of *d*-amphetamine. Two-way mixed model analysis of variance (sex and dose) and planned comparisons were used in the statistical analyses.

Results—The low dose of *d*-amphetamine functioned as a reinforcer in women but not men whereas the high dose of *d*-amphetamine functioned as a reinforcer in men but not women. Men self-administered significantly more capsules under the high dose condition than women.

Conclusion—The results of this study suggest that men are more sensitive to the reinforcing effects of a high dose of *d*-amphetamine than women. Future research is needed that prospectively determines the reinforcing effects of weight-adjusted doses of *d*-amphetamine in women and men while controlling for menstrual cycle phase.

INTRODUCTION

The reinforcing effects of stimulants may differ as a function of sex. Findings from preclinical non-human animal studies indicate that female rats meet cocaine self-administration acquisition criteria faster, escalate drug intake more quickly and a greater percentage of female rats meet acquisition criteria than male rats (1,2,3,4). In addition, female rats reach higher break points on a progressive-ratio schedule of cocaine reinforcement than male rats (1,5). Results of human laboratory studies are mixed regarding sex differences in the reinforcing effects of stimulants. The results of one study suggest that men are more sensitive to the reinforcing effects of stimulants (6). The results of another study suggest that women are more sensitive to the reinforcing effects of stimulants (7). No sex differences in the reinforcing effects of stimulants were reported in other studies

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(8,9,10). Understanding human sex differences in the reinforcing effects of drugs may inform drug prevention and treatment efforts by providing the information necessary to tailor sex- or gender-specific programs.

The purpose of the present study was to examine human sex differences in *d*-amphetamine self-administration using a modified progressive-ratio schedule of reinforcement. Data from three studies that employed similar progressive-ratio procedures were combined (11,12,13). The behavioral and cardiovascular effects of *d*-amphetamine were assessed in 10 women and 15 men.

METHODS

Data from three studies (11,12,13) in which, participants worked for capsules containing *d*-amphetamine (low [8–10 mg] and high [16–20 mg]) or placebo on a modified progressive-ratio procedure were included in this analysis. The Institutional Review Board of the University of Kentucky Medical Center approved the conduct of two studies (12,13) and the Institutional Review Board of the University of Mississippi Medical Center approved the conduct of the other study (11).

Participants

Twenty-five participants (15 men, 10 women) were included in this analysis (see Table 1 for demographic information). None of the participants were drug naive. One study (12) required that participants report past month recreational use of a stimulant. Participants completed two practice sessions. All volunteers gave their sober, written informed consent. Potential volunteers with histories of or current physical disease or serious psychiatric disorder (were excluded.

Experimental Sessions

Expired air samples were negative for alcohol. Urine samples were negative for benzodiazepines, barbiturates, cocaine, opioids and pregnancy. Participants also passed a field sobriety test prior to experimental sessions. If a participant was positive for amphetamine or THC, key study personnel decided whether to let them participate that day.

Sampling Sessions—Volunteers were administered eight identical capsules containing placebo or *d*-amphetamine (low [8–10 mg] or high [16–20 mg]). Participants were instructed to pay attention to and make notes about the effects of the drug, because in a future session they would be offered the opportunity to work to receive that drug again. After ingesting capsules, volunteers completed questionnaires and cardiovascular measures at hourly intervals for several hours.

Self-Administration Sessions—Self-administration sessions differed from sampling sessions only in that volunteers had to earn capsules by responding on a modified progressive-ratio procedure (14,15,16,17).

Modified Progressive-Ratio Procedure

The modified progressive-ratio procedure has been used previously and is a sensitive measure of drug reinforcement in humans (e.g., 11,12,14,15,18,19). This procedure has been modified so that subjects receive a fraction of the previously sampled dose for each ratio completed and drug is delivered when responding has ceased. Volunteers were able to respond on a computer mouse or keyboard to earn all, some or none, of the capsules that were administered during the preceding sampling session. A total of eight opportunities were available for volunteers to self-administer a fraction (i.e. $1/8^{th}$) of the previously

sampled dose. Prior to each opportunity, volunteers were asked if they wanted to work for a capsule. If the volunteer responded YES, they were required to click the mouse a predetermined number of times to earn the capsule. To earn the first capsule, volunteers were required to click the mouse 50 times (11,12) or 25 times (13). To earn each additional capsule, the number of required responses subsequently doubled. If the volunteer responded NO the task was terminated.

Subject-Rated Drug-Effect Questionnaires and Cardiovascular Measures

The Addiction Research Center Inventory (20) and a locally developed Drug-Effect Questionnaire (21) were administered on a computer. Cardiovascular measures were recorded using automated vital signs monitoring equipment.

Drug Administration

Doses were prepared using commercially available *d*-amphetamine. In one study each capsule contained 0 mg (placebo), 1.25 mg (10 mg dose), or 2.5 mg (20 mg dose) *d*-amphetamine (11). In two studies each capsule contained 0 mg (placebo), 1 mg (8 mg dose), or 2 mg (16 mg dose) *d*-amphetamine (12,13). Cornstarch or lactose was used as filler.

Data Analysis

Demographic data were compared using unpaired t-tests ($p \leq 0.05$). A Bonferroni correction was used to determine the alpha level for each test (e.g. 22,23). Effects were considered significant for $p \leq 0.05$ for the modified progressive-ratio procedure and cardiovascular measures. Effects were considered significant for $p \leq 0.01$ and 0.003 for the ARCI and Drug Effect Questionnaire, respectively.

The dependent measure on the modified progressive-ratio procedure was the number of capsules earned. Data from the progressive-ratio task were analyzed by a two-factor repeated-measure analysis of variance (ANOVA). The factors were Sex (male or female) and Dose (placebo, low or high dose *d*-amphetamine). Tukey's Honestly Significant Difference (HSD) *post hoc* tests were conducted using weighted means due to unequal group sizes (i.e. 10 women and 15 men). Data for the subject-rated drug effect questionnaires and cardiovascular measures, collected during sampling sessions, was analyzed in a similar fashion.

RESULTS

Progressive-Ratio

A significant main effect of dose was revealed on the number of capsules administered ($F_{23, 2} = 4.2$, $p < 0.05$). Tukey's HSD revealed that women self-administered a greater number of low-dose *d*-amphetamine capsules and men self-administered a greater number of high-dose *d*-amphetamine capsules than placebo. Tukey's HSD also revealed that men earned a significantly greater number of capsules under the high-dose *d*-amphetamine condition than women (Figure 1).

Subject-Rated Drug-Effect Questionnaires

d-Amphetamine significantly increased scores on two scales from the ARCI: A ($F_{23, 2} = 4.8$, $p < 0.01$) and MBG ($F_{23, 2} = 7.3$, $p < 0.01$). Women and men did not differ on the A scale. Tukey's HSD revealed that women reported significantly higher scores on the MBG scale than the men, regardless of dose.

d-Amphetamine increased ratings of "active-alert-energetic" ($F_{23, 2} = 12.9$, $p < 0.003$), "like drug" ($F_{23, 2} = 7.0$, $p < 0.003$) and "willing to take again" ($F_{23, 2} = 8.4$, $p < 0.003$) from the Drug-Effect Questionnaire (see Figure 1 for ratings of "like drug" and "take again"). Women and men did not differ on these items.

Cardiovascular Measures

A main effect of dose was found on heart rate ($F_{23, 2} = 5.2$, $p < 0.05$). Heart rate did not vary as a function of sex. A main effect of dose ($F_{23, 2} = 19.0$, $p < 0.05$) and sex ($F_{23, 2} = 10.6$, $p < 0.05$) was found on systolic pressure. Systolic pressure was higher in men relative to women, regardless of dose.

DISCUSSION

To the best of our knowledge, this is the first report of human sex differences in *d*-amphetamine self-administration using a progressive-ratio schedule of reinforcement. The results of this retrospective analysis demonstrate that women and men differ with regard to *d*-amphetamine self-administration. Low dose *d*-amphetamine functioned as a reinforcer in women whereas high dose *d*-amphetamine functioned as a reinforcer in men. Men also earned a significantly greater number of capsules under the high dose *d*-amphetamine condition than women.

Previous studies that assessed the reinforcing effects of stimulants in humans as a function of sex have yielded mixed results (6,7,8,9,10). In one study, men chose ephedrine on approximately 33% of occasions whereas women chose it on less than 10% of occasions (6). In another study a greater proportion of women were choosers of *d*-amphetamine (54%) than men (46%) (7). No difference was found between men and women in terms of drug choice in other studies (8,9,10). The progressive-ratio procedure used in the current analysis may be sensitive to individual differences in the reinforcing effects of stimulants (24,25). One study revealed differences between high and low sensation seekers in *d*-amphetamine self-administration using a modified progressive-ratio procedure (24). This method could be useful for predicting the likelihood of abuse of a drug within a specific demographic. Future studies should seek to establish the utility of this procedure in assessing individual differences in the reinforcing effects of drugs.

In the current analysis, men and women differed with regard to *d*-amphetamine self-administration. At least three caveats should be considered. First, this study was conducted retrospectively and combined data from experiments that used slightly different progressive-ratio schedules and different doses of *d*-amphetamine. Second, the women included in this analysis weighed significantly less than the men and, as a result, may have received functionally higher doses of *d*-amphetamine. Whether the observed difference between women and men was the result of a quantitative difference in the dose-response functions or an inherent difference in the reinforcing effects of *d*-amphetamine cannot be gleaned from this study. Future studies should examine the reinforcing effects of a range of weight-adjusted doses of *d*-amphetamine in women and men. Finally, menstrual cycle phase or circulating hormone levels of the women included in this analysis were not monitored. Several studies have demonstrated that women are more sensitive to the effects of stimulants during the follicular phase of the menstrual cycle when circulating estrogen levels are high and progesterone levels are low (e.g. 26). Interpretation of results for the current study is limited because women were cycling at different times. Future studies should prospectively examine human sex differences in stimulant self-administration while controlling for circulating hormone levels.

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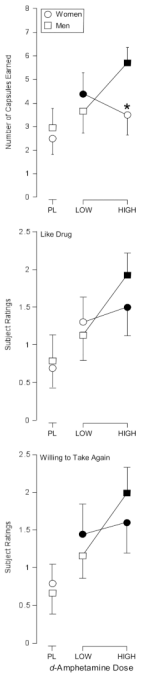

Figure 1.

Dose response functions for number of capsules earned on the modified progressive ratio procedure during self-administration sessions (Top Panel); subject ratings of Like Drug (Middle Panel); and Wiling to Take Again (Bottom Panel) from the Drug-Effect Questionnaire collected during sampling sessions. X-axes: *d*-Amphetamine dose. Data points show means of 10 women (circles) and 15 men (squares). Data points above PL represent placebo. Filled symbols indicate the data point is significantly different from the corresponding placebo value. An asterisk indicates that women and men were significantly different from each other at that dose. Unidirectional brackets represent one standard error of the mean.

Table 1

Demographic information for the 10 women and 15 men included in the analysis. Means and standard deviations are presented for age, years of education, body weight, body mass index (BMI), number of alcohol drinks per week, caffeine (mg) consumed per day, and number of cigarettes smoked per day.

Sex	Age	Years of Education	Weight (kg)	BMI	Alcohol Drinks/ week	Caffeine (mg/day)	Cigarettes/ day
Women N = 10	27 ± 5	13 ± 3	67 ± 15	24 ± 4	4 ± 5	130 ± 129	9 ± 7
Men N = 15	26 ± 9	13 ± 1	79 ± 15	24 ± 4	9 ± 8	141 ± 178	9 ± 9

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