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Similar discriminative-stimulus effects of D-amphetamine in women and men

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Abstract

The results of controlled non-human animal and human laboratory studies are mixed regarding whether women and men respond differently to stimulant drugs. In order to assess potential gender differences in the effects of D-amphetamine, we conducted a retrospective analysis of six studies conducted in our laboratory that used identical procedures and measures. Thirteen women and fourteen men learned to discriminate 15 mg oral D-amphetamine. After acquiring the discrimination (i.e., ≥80% correct responding on 4 consecutive sessions), the effects of a range of doses of D-amphetamine (0, 2.5, 5, 10, and 15 mg) alone and in combination with other drugs, were assessed. Only data from sessions in which D-amphetamine was administered alone were included in this analysis. D-Amphetamine functioned as a discriminative stimulus and dose-dependently increased drug-appropriate responding. Women and men did not differ in their ability to discriminate D-amphetamine. Women and men differed on participant-ratings of high (women < men), nausea (women > men) and sluggish (women < men), women also experienced greater increases in diastolic pressure than men. Because the results of this study may have been confounded by the training procedures, future research should use other behavioral arrangements (e.g. drug self-administration) to determine if women and men respond differently to the effects of D-amphetamine.

Keywords: Amphetamine; Drug discrimination; Sex; Subjective effects; Cardiovascular effects

1. Introduction

Results from epidemiological studies suggest that women may be more vulnerable to stimulant (e.g. cocaine or methamphetamine) dependence than men (e.g. Brecht et al., 2004; Westermeyer and Boedicker, 2000). For example, in one sample of 350 methamphetamine abusers (56% male), women advanced to regular use, defined as using 3 or more days per week, more quickly than men (1.6 years and 2.6 years, respectively) and entered treatment after fewer years of drug use (8.8 years and 9.7 years, respectively) (Brecht et al., 2004). In another sample of 642 patients (57% male) admitted to a treatment program, women reported using cocaine for fewer years prior to entry than men (2.8 vs. 4 years, respectively). In addition, women in that sample were diagnosed with cocaine abuse or dependence at higher rates than men (13% vs. 7%, respectively) (Westermeyer and Boedicker, 2000). Finally, data collected from 1047 prescription stimulant abusers (60% male) between 1995 and 1998 revealed that women were 2.6 times more likely to develop prescription stimulant dependence than men (Wu and Schlenger, 2003). The aforementioned studies suggest that women may be more susceptible to stimulant abuse and dependence than men. The biological, behavioral or sociocultural variables that mediate these differences are not known. Perhaps women are more likely to seek treatment than men. Alternatively, the behavioral effects of stimulants may be more robust in women than men.

Results from pre-clinical laboratory studies are mixed regarding differences between females and males in terms of behavioral responses to stimulants. Several studies have demonstrated that female rats acquire drug self-administration more rapidly and escalate drug intake more quickly than male rats, regardless of estrous cycle phase (e.g. Festa et al., 2004; Lynch and Carroll, 1999; Roth and Carroll, 2004). In one study,

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for example, female rats acquired cocaine self-administration (i.e. >100 infusions in a 6 h period over five consecutive sessions) significantly faster than male rats (7.6 vs. 16.7 days, respectively) (Lynch and Carroll, 1999). A larger percentage of female rats also met self-administration acquisition criteria than male rats (70% vs. 30%, respectively) (Lynch and Carroll, 1999). The results of other studies, by contrast, suggest that there are few, if any, differences between male and female rats (Anderson and van Haaren, 1999; Caine et al., 2004; Craft and Stratmann, 1996; Stratmann and Craft, 1997; Haney et al., 1995). Two studies, for instance, failed to find sex differences in the discriminative-stimulus effects of cocaine in rats (Anderson and van Haaren, 1999; Craft and Stratmann, 1996).

Consistent with the pre-clinical laboratory data, results from human laboratory studies are also mixed. Results from several studies suggest that men may be more sensitive to the behavioral and physiological effects of stimulants such as D-amphetamine and cocaine (e.g. Lukas et al., 1996; Sofuoglu et al., 1999, 2000; White et al., 2002). In one study, for example, men achieved significantly higher plasma cocaine levels and reported a greater number of euphoric events compared to women following administration of 0.9 mg/kg intranasal cocaine (Lukas et al., 1996). The results from other human laboratory studies, by contrast, suggest that women may have a more robust response to stimulants than men (e.g. Evans et al., 1999; Kosten et al., 1996; McCance-Katz et al., 2005; Singha et al., 2000). For example, following administration of 80 mg/kg oral cocaine, women reported higher ratings of "bad drug effect" and "nervous" compared to men (Singha et al., 2000).

Given the mixed results described above, the present retrospective analysis was conducted to examine possible gender differences in responses to D-amphetamine. Data from six studies that used identical drug-discrimination procedures were combined. Each of the studies was designed as a pretreatment study in which D-amphetamine was given in combination with another drug. D-Amphetamine alone was common to all studies and data collected from sessions in which drug combinations were administered were not included in this retrospective analysis. The discriminative-stimulus effects of D-amphetamine (0, 2.5, 5, 10 and 15 mg) were assessed in 13 women and 14 men with a history of non-therapeutic stimulant use. A drug (15 mg D-amphetamine) versus not drug (placebo) discrimination procedure was utilized in each study. To the best of our knowledge, this is the first analysis of gender differences in the discriminative-stimulus effects of D-amphetamine in humans. In order to more fully assess potential gender differences in response to D-amphetamine, data from self-report questionnaires, a performance task, and cardiovascular measures were also analyzed.

2. Methods

Six studies were included in this retrospective analysis (Lile et al. 2005a,b; Rush et al., 2003, 2004; Stoops et al., unpublished data, 2006a). Each study was designed as a pretreatment study in which D-amphetamine was given in combination with risperidone (Rush et al., 2003), alprazolam (Rush et al., 2004), aripiprazole (Lile et al., 2005a; Stoops et al., 2006a), oxazepam (Lile et al., 2005b), or fluphenazine (Stoops et al., unpublished data). In all studies, medications were administered acutely and a minimum of 24 h separated all drug administrations. Data collected from sessions in which drug combinations were administered are not included in this analysis. All studies employed identical experimental procedures and were conducted in the same laboratory. The Institutional Review Board at the University of Kentucky approved all protocols and informed consent documents.

2.1. Participants

Thirteen adult women and 14 adult men that were recruited via newspaper ads, flyers, and word-of-mouth participated and were included in this analysis. If a participant had enrolled in more than one of the studies, only data from the first study in which they participated was used. Participants were paid $40/session to participate in addition to performance-based payment as outlined below. Participants provided written informed consent, and completed questionnaires assessing drug use, medical and psychiatric histories, prior to participating. All participants were in good physical and psychiatric health as determined by the medical and psychiatric questionnaires, and clinical laboratory chemistries. Participants were without contraindications to D-amphetamine. Drug urine screens conducted during screening were negative for benzodiazepines, barbiturates, cocaine, and opioids (Abuscreen ONTRAK, Roche Diagnostic Systems, Nutley, NJ). In the female participants, urine pregnancy tests before study participation and prior to each session had to be negative.

2.2. General procedures

Participants enrolled as outpatients at the Laboratory of Human Behavioral Pharmacology at the University of Kentucky, Monday through Friday, for up to 37 experimental sessions. Sessions typically began between 8:00 am and 10:00 am. The time of day that sessions were conducted was held constant for each volunteer. Participants were informed that during their participation they would receive a stimulant like D-amphetamine (Dexedrine®, Glaxosmithkline, Research Triangle Park, NC) or a placebo. For each study, participants also received another drug alone or in combination with D-amphetamine during some sessions. As noted above, data from these sessions were not included in the analyses. Participants were told that the purpose of the study was to determine if they could detect the presence of a drug and how the drug affects mood and behavior. Other than receiving this general information, participants were blind to the type of drug administered and were given no instructions regarding what they were "supposed" to do or what outcomes might be expected.

Prior to initiating drug testing, participants completed two "practice" sessions. These practice sessions were used to familiarize participants with the drug-discrimination task, participant-rated drug-effect questionnaires, performance measure, and daily laboratory routine. No medications were administered on these days.