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Human Response to Repeated Low-Dose d-Amphetamine:

Evidence for Behavioral Enhancement and Tolerance

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Previously, we reported progressively greater behavioral responses to repeated d-amphetamine in human subjects that represented a potential model of behavioral sensitization. To extend this work, 59 healthy volunteers were randomly assigned to one of three protocols: (1) placebo administered on days 1, 3, and 5 (PPP); (2) placebo administered on days 1 and 3, and d-amphetamine (0.25 mg/kg) on day 5 (PPA); and (3) d-amphetamine administered on days 1, 3, and 5 (AAA). Comparisons were made among the three groups to determine whether repeated d-amphetamine produced an increased behavioral response. Subjective ratings of vigor and euphoria exhibited the greatest response following the third dose of the AAA group, as hypothesized. In contrast, drug liking was greatest following a single or first d-amphetamine dose. These effects were greater in women. Progressive changes in subjective responses following repeated d-amphetamine administration may occur in healthy human subjects, although this effect may be greater for women.
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KEY WORDS: *d-Amphetamine; Sensitization; Human subjects; Placebo-controlled; Double-blind, Drug liking*

Behavioral sensitization is a progressively greater and enduring behavioral response that occurs following repeated stimulant administration. This phenomenon has been widely studied in animals and has been hypothesized to underlie aspects of human stimulant addiction, as well as several psychiatric syndromes (Robinson and Becker 1986; Robinson and Berridge 1993). Despite the potential importance of behavioral sensitization in human clinical conditions, few controlled human studies of this process have been reported.

During the past several years, we have investigated whether repeated low-dose d-amphetamine leads to a progressive behavioral response when administered to human volunteers, consistent with a behavioral sensitization model. In the first 4-day study, 11 healthy subjects were given two oral doses of d-amphetamine (0.25 mg/kg) at 48-hour intervals alternating with two similarly spaced, matched placebo doses (Strakowski et al. 1996). Subjects exhibited significantly greater eye blink rates and changes in energy level, mood, and talkativeness following the second d-amphetamine dose as compared to the first amphetamine and both placebo doses. In a separate study of 11 different healthy subjects, three oral doses of d-amphetamine (0.25 mg/kg) were administered at 48-hour intervals again alternating

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with three matched placebo doses (Strakowski and Sax 1998). Eye-blink rate, elevated mood, talkativeness, and motor activity were progressively increased following each d-amphetamine dose as compared to the other conditions. This progression of response was found to be associated with high levels of novelty seeking in personality assessments, indicating that certain individual characteristics may alter the human response to repeated stimulant administration (Sax and Strakowski 1998). Finally, we completed a two-dose study in unmedicated patients with new-onset, mild-to-moderate psychotic symptoms and observed no progression in behavioral responses following a second low-dose of d-amphetamine, in contrast to our findings in healthy subjects (Strakowski et al. 1997). One interpretation of this finding is that by the time psychosis develops, patients are fully sensitized from the processes causing psychosis such that additional behavioral progression cannot occur.

Two other groups used similar controlled studies to examine the human response to repeated stimulant administration. Rothman et al. (1994) examined the effects of repeated intravenous (IV) cocaine challenges in subjects with a recent history of IV cocaine use. They observed no progression in response to repeated cocaine exposure among these subjects. These results suggest that people with cocaine abuse or dependence have been sensitized such that additional progression of responses to stimulants does not occur. More recently, Wachtel and deWit (1999) used a 4-day study design in which 16 healthy volunteers were administered two doses of d-amphetamine (20 mg) at 48-hour intervals alternating with placebo. In contrast to our findings (Strakowski et al. 1996), they observed no progression of behavioral responses.

Our previous within-subject study designs Strakowski et al. (1996); Strakowski and Sax (1998), and that of Wachtel and deWit (1999), expose subjects to both placebo and amphetamine so that they may be able to break the study blind. Similarly, the raters in these studies observe the same individuals following both placebo and stimulant administrations, which could influence results based on rater expectations. These limitations may explain differences between our results (Strakowski et al. 1996; Strakowski and Sax 1998) and those of Wachtel and deWit (1999).The current study was specifically designed to minimize these limitations. First, a parallel group, double-blind, placebo-controlled design was used to protect the blind better. Second, the primary ratings were self-reports to eliminate potential bias by raters familiar with previous studies and hypothesized results. With these safeguards, we tested the hypothesis that subjects who received two prior d-amphetamine doses would exhibit a greater response on the primary measures following a third dose than subjects receiving a single d-amphetamine dose or placebo.

METHODS

Protocol Summary

Fifty-eight subjects were randomly assigned to one of three treatment groups in which d-amphetamine 0.25 mg/kg or matched placebo capsules were orally administered once every 48 hours (i.e., at 10 A.M. on days 1, 3, and 5) during a 5-day protocol. The three treatments conditions were: (1) placebo administered on days 1, 3, and 5 (PPP); (2) placebo administered on days 1 and 3, and d-amphetamine administered on day 5 (PPA); and (3) amphetamine administered on days 1, 3, and 5 (AAA). Raters and subjects were blind to the treatment group assignment. Subjective ratings of d-amphetamine effects and eye-blink rate were measured hourly following drug and placebo administration. Comparisons were performed among the three treatment groups to determine whether repeated dosing of d-amphetamine was associated with increased behavioral responses.

Subjects

Sixty-two healthy men and women volunteers were recruited by advertisements and word of mouth to participate in this study. All of these subjects provided written informed consent after the study procedures, and risks were fully explained. This protocol was reviewed and approved by the Institutional Review Board of the University of Cincinnati. All subjects met the following inclusion criteria: (1) age 18–45 years; (2) no history of major DSM-IV psychiatric disorders including psychoactive substance dependence or abuse; (3) no recent drug or significant alcohol use as assessed using the Addiction Severity Index (ASI); (4) no history of major medical or neurological illness; (5) no previous major stimulant use (i.e., d-amphetamine, cocaine, methamphetamine, methylphenidate) including diet pills; (6) no current use of medications with central nervous system effects; (7) if female, not pregnant as demonstrated by a negative serum pregnancy test; (8) English speaking; (9) no family history of an alcohol or substance use disorder as defined in DSM-IV; and (10) no history of nicotine dependence. Four subjects were dropped from analysis. One subject had a positive urine toxicology screen for amphetamine, so was removed. Another was dropped after developing a febrile viral illness during the protocol. Two additional subjects were removed secondary to concerns about lack of effort and inability to follow instructions, leaving a total of 58 healthy volunteers who completed this study. These subjects included 28 women and 30 men, who had a mean (±SD) age of 25 (±4) years and were 74% ($n = 43$) Caucasian. There were no differences among treatment groups in any demographic variables. Subjects were paid for their participation.

The psychiatric and substance abuse evaluations were performed using the Structured Clinical Interview for DSM-IV (SCID-P) and the Addiction Severity Index (ASI; McLellan et al. 1992) completed by a psychiatrist (SMS, MPD, CMA) or trained Ph.D. psychologist (KWS). Medical histories were obtained from a medical review of systems, a physical exam, routine laboratory studies, an EKG, and a pregnancy test in women. Urine toxicology screens were obtained at the initial screening and repeated each morning before receiving amphetamine or placebo.

Experimental Design

Subjects received a fixed oral dose of d-amphetamine (0.25 mg/kg) or a matched placebo capsule every other day for 5 days. Therefore, each subject received a total of three drug or placebo doses on days 1, 3, and 5 of the protocol according to their randomly assigned treatment group. The second and fourth days involved no study procedures. Subjects and all study personnel except for one physician were blind to group assignment. The unblinded physician dispensed the medications but had no other contact with the subjects.

The subjects were randomly assigned to one of three treatment groups. Randomization was stratified by sex, because animal studies suggest sex may influence the development of sensitization (Robinson and Becker 1986). Subjects randomized to the experimental, three d-amphetamine dose (AAA), group received an oral dose of d-amphetamine (0.25 mg/kg) on each of the 3 study days (i.e., protocol days 1, 3, and 5). This group was hypothesized to demonstrate a progression in behavioral response following repeated d-amphetamine exposure. The first control condition consisted of subjects randomized to receive a single placebo dose on each of the 3 study days (PPP group). This group controlled for the effects on behavioral responses of simply participating in the protocol. The second control group consisted of subjects randomized to receive a placebo dose on protocol days 1 and 3 and then a dose of d-amphetamine (0.25 mg/kg) on day 5 (PPA group). This group controlled for the effects on behavioral measures of a single d-amphetamine dose on the fifth study day. Nineteen subjects (10 men, 9 women) were randomized to each of the AAA and PPP groups. Twenty subjects (10 men, 10 women) were randomized to the PPA group.On each study day before receiving drug or placebo, a urine toxicology screen was obtained to verify that subjects were not using psychoactive substances. Then at approximately 9:30 A.M. baseline self-report ratings, eye-blink rate, and vital signs were obtained. Placebo or d-amphetamine, according to group assignment, was administered 90 minutes later, and then ratings and vital signs were obtained hourly for 5 hours. The number of spontaneous eye blinks were counted for 5 minutes each hour. To obtain these ratings, subjects were videotaped while being interviewed about subjective effects of d-amphetamine. They were not informed that the eye-blink measurement was occurring. The order of the videotapes was then scrambled, and eye blinks were counted by trained raters (inter-rater reliability, kappa$>$0.90) who were blinded to the intent and hypotheses of the study. Spontaneous eye blinking is associated with central dopaminergic activity and demonstrated progressive increases in our previous studies of repeated d-amphetamine effects (Strakowski et al. 1996; Strakowski and Sax 1998).Self-reported subjective drug effects were assessed hourly using the Profile of Mood States (POMS; McNair et al. 1992) and the Addiction Research Center Inventory (ARCI; Haertzen and Hickey 1987). Both of these instruments are well-established self-report scales of subjective responses to drug administration. The Vigor subscale of the POMS was analyzed as a measure of subjective activation expected to be responsive to d-amphetamine (McNair et al. 1992). This subscale score was calculated by summing the designated items from the 65-item POMS as instructed by the POMS manual. The ARCI MBG (euphoria) scale was specifically developed for measuring euphorigenic effects of stimulants, so was also examined (Haertzen and Hickey 1987; Wachtel and de Wit 1999). When completing these ratings, subjects were asked to score each item for "how they feel *now*" (at the hourly sessions). In addition, ratings of drug "liking" from the Drug Effects Questionnaire (Rush et al. 1995) were obtained. This 9-point ordinal scale rates how much subjects like a drug effect "right now." Responses vary from "-4 = dislike very much" to "4 = like very much." Finally, during each session, subjects were asked to guess whether they thought they had received d-amphetamine or placebo. The final rating for each day was used to examine whether the blind was protected.

Statistical Analysis

All data were double-entered, cross-checked for accuracy, and then stored in an Access Database (Microsoft, Redmond, WA). All statistical analyses were performed using the Statistical Analysis System for the Personal computer (SAS Institute, Cary, NC). Changes from baseline at each hour were summed for each measurement providing an over-all "area-under the curve" (AUC) score for each study day. To test the hypothesis directly that behavioral measurements would be increased following repeated d-amphetamine exposure as compared to a single dose and placebo, the AUCs for each behavioral measurement for each treatment group on day 5 were compared using analysis of variance (ANOVA). Protected *t*-tests were then used for multiple comparisons to determine specific treatment group effects. As second-

ary analyses, sex-by-group interactions were examined. Other analyses were performed for completeness.

RESULTS

Subjective self-rated responses in this study are illustrated in Figure 1. The POMS Vigor response (total AUC) on the final study day (day 5; Figure 1, top) significantly differed among groups [F(2,55) = 4.9, p = .01]. Specifically, the response of the AAA group was significantly greater than both of the other groups ($p <$ .05). The ARCI MBG response (total AUC) on the final study day (Figure 1, middle) differed among groups (statistical trend) [F(2,55) = 3.0, $p < .06$]. The response of the AAA group was significantly greater than that of the PPP group ($p < .05$), but not significantly different from the PPA group ($p > .6$). Finally, the DEQ "drug liking" response (total AUC) on the final study day (Figure 1, bottom) was significantly different among groups [F(2,55) = 3.3, $p < .05$]. The response of the PPA group was significantly greater than the PPP group ($p < .05$) and nonsignificantly greater than the AAA group ($p < .09$). Notably, the DEQ drug liking response on the first d-amphetamine administration (day 1) in the AAA group (4.6, SE = 0.9) was similar to the d-amphetamine response on day 5 of the PPA group (4.5, SE = 1.2; Figure 1, bottom). Moreover, the DEQ drug-liking response following the first d-amphetamine administration in the AAA group was significantly greater on the first dose than the second (t = 2.4, p = .03), and third (t = 2.6, p = .02) doses in that group. In contrast to subjective measures, the eye-blink response did not differ among groups [F(2,55) = 1.3, $p > .2$; Figure 3]. In this trial, a total of 39 patients received 77 doses of d-amphetamine in the AAA and PPA groups. Overall, these subjects correctly guessed that they had received d-amphetamine 44 times (57%) and incorrectly guessed that they had received placebo the remaining 33 times (43%). This rate of guessing was not significantly better than chance (i.e., 50% for each; $\chi^2 = 0.8$, df = 1, $p > .3$) and did not differ by sex ($\chi^2 < 0.01$, df = 1, p = .95). On the final study day, the subjects in the PPA group were significantly more likely to guess correctly they had received d-amphetamine (n = 15, 75%) than those in the AAA group (n = 8, 42%; $\chi^2 = 4.4$, df = 1, p = .04). Within the AAA group, subjects were more likely to guess correctly they had received d-amphetamine following the first dose (n = 14/19, 74%) than the remaining two doses (n = 15/38, 39%; $\chi^2 = 6.0$, df = 2, p = .05). No subjects experienced any significant adverse events from participating in this study.

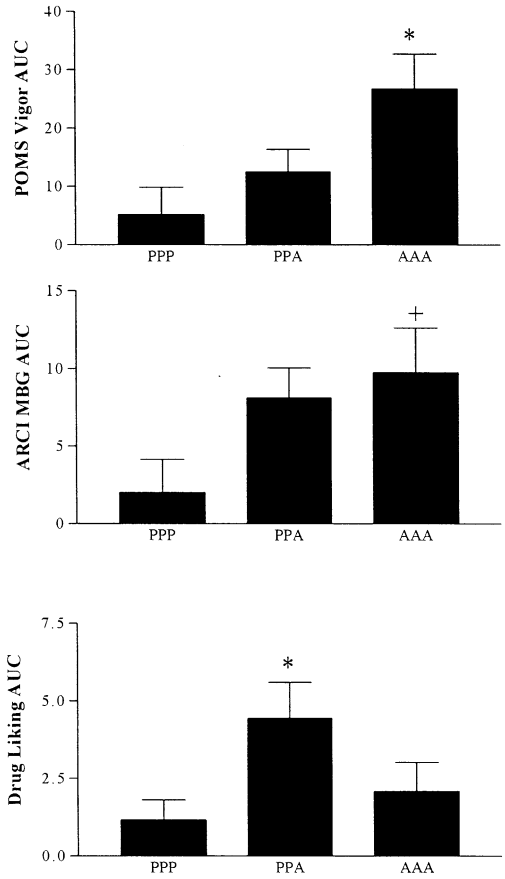

Figure 1. Total change in subjective ratings from baseline (area under the curve, AUC) for the POMS Vigor, ARCI euphoria (MBG), and DEQ drug liking ratings on the final day of drug/placebo administration (day 5) for the three placebo (PPP), two placebo, and a final d-amphetamine (PPA) and three d-amphetamine (AAA) administration conditions. An asterisk (*) indicates a significant difference ($p <$ .05) from both of the other two groups. A cross (+) indicates a significant difference from the PPP group.

Sex Effects

For the POMS Vigor response on day 5, a significant sex-by-group interaction was observed [F(5,52) = 3.1, $p < .02$; Figure 2, top]. Specifically, the POMS Vigor response for women in the AAA group was significantly greater than this response for men in the AAA group ($p < .03$). In addition, the POMS Vigor response for women in the AAA group was significantly greater than the change in this rating for all other sex-by-group conditions (e.g., women in the PPA group or men in the PPP group; range of p-values was $<.01$ to $<.001$ for these comparisons). In contrast, the change in POMS vigor for men in the AAA group exhibited no difference from the change in any other sex-by-group condition ($p > .2$).For the ARCI MBG response on day 5, a possible sex-by-group interaction was observed [F(5,52) = 2.3, p = .057; Figure 2, middle]. Specifically, the ARCI MBG response for women in the AAA group was significantly greater than this response for men in the AAA group ($p < .03$) and for both sex-by-placebo (PPP)

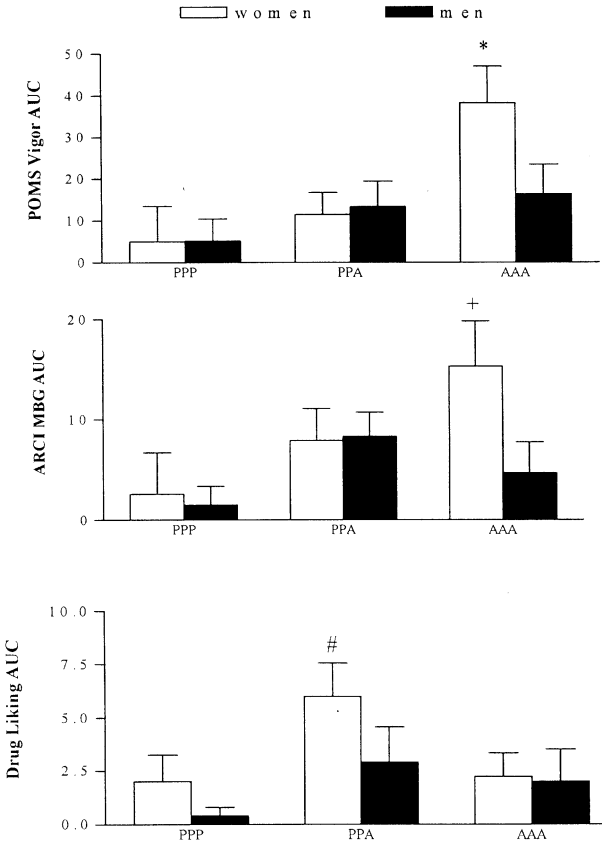

Figure 2. Total change, by sex, in subjective ratings from baseline (area under the curve, AUC) for the POMS vigor, ARCI euphoria (MBG), and DEQ drug-liking ratings on the final day of drug/placebo administration (day 5) for the three placebo (PPP), two placebo and a final d-amphetamine (PPA), and three d-amphetamine (AAA) administration conditions. An asterisk (*) indicates a significant difference ($p < .05$) from all other sex-by-group conditions. A cross (+) indicates a significant difference ($p < .05$) from the men's AAA and both PPP groups. A number sign (#) indicates a significant difference ($p < .05$) from all other sex-by-group conditions, except the men's PPA group.

conditions ($p < .01$). As with POMS Vigor, the ARCI MBG response for men in the AAA group showed no significant differences in this rating from any other sex-by-group condition ($p > .4$).

For the DEQ drug-liking response on day 5, the sex-by-group interaction demonstrated only a trend toward a statistical difference [$F(5,52) = 2.0$, $p < .09$; Figure 2, bottom], but for completeness, the results are presented. Follow-up t-tests suggested that the change in drug-liking scores for women in the PPA group was nonsignificantly greater than the drug-liking response for men in that group ($p < .1$). However, the drug-liking response in women of the PPA group (day 5) was significantly greater than all other sex-by-group conditions (e.g., men in the AAA group, or women in the PPP group; the range of p-values was $< .05$ to $< .005$ for these comparisons). Again, in contrast, the drug-liking response for the men in the PPA group exhibited no significant difference from the change in this score in any other sex-by-group condition ($p > .15$ in all cases).

Finally, for eye blinks, no sex-by-group interaction was observed [$F(5,52) = 1.1$, $p > .4$; Figure 3, bottom].

DISCUSSION

In this study, we extended previous work that examined the human response to repeated low-dose d-amphetamine by using a parallel-group study design and self-report response measures designed to protect the blind between d-amphetamine and placebo better, as well as to minimize rater bias. Our results suggest that some subjective responses, particularly in women, may progressively increase following repeated d-amphetamine exposure. Specifically, the POMS Vigor and, perhaps, the ARCI euphoria (MBG) ratings both exhibited an increase following a third dose of d-amphetamine as compared to a single dose or placebo. In contrast, other subjective responses seemed to exhibit tolerance. Specifically, the first d-amphetamine dose produced a

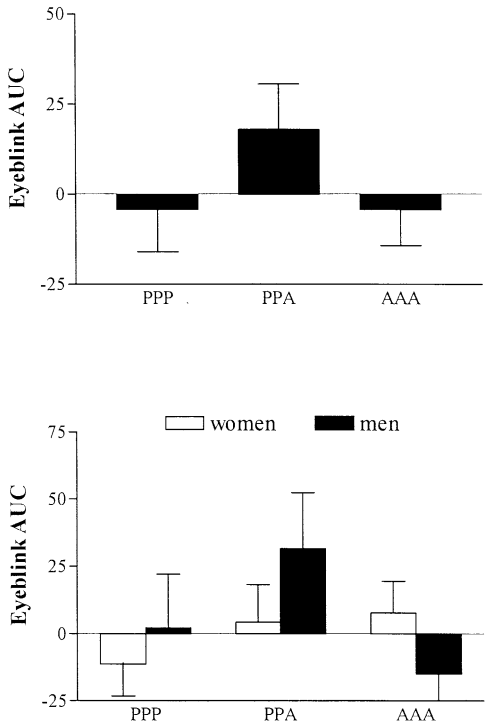

Figure 3. Total change in eye-blink rate from baseline (area under the curve, AUC) on the final day of drug/placebo administration (day 5) for the three placebo (PPP), two placebo and a final d-amphetamine (PPA), and three d-amphetamine (AAA) administration conditions (top) and by sex (bottom). No significant differences among conditions were observed.

greater response in subjective ratings of drug liking than the third d-amphetamine dose or placebo. Again, this effect was observed primarily in women. In general, the study design provided good protection of the blind, because subjects were unable to guess correctly when they had received d-amphetamine better than chance. Nonetheless, the subjects were better at guessing that they had received d-amphetamine after the first (in the AAA group) or single (in the PPA group) dose conditions than after a second or third dose. This suggests that the subjects' perception of drug effect, similar to the drug-liking response, diminished with repeated exposure and that the increases observed in the POMS Vigor rating were not merely in response to perceived drug or placebo administration. Together, these results suggest that different subjective effects of d-amphetamine may be mediated through separate neurobehavioral mechanisms, such that some effects exhibit enhancement with repeated dosing; whereas, others develop tolerance.

Robinson and Berridge (1993) observed that people with stimulant dependence continue to abuse stimulants long after they seem to receive any particular pleasure or liking from the experience. They proposed that stimulant dependence develops from a sensitization in the "incentive salience" (or "wanting") of drugs, that is separate from the actual experience of enjoying the drug effect (to which tolerance develops). Our observations in this study are consistent with this model, although it is not possible to extrapolate directly changes in self-report ratings in subjects who have received only three low doses of d-amphetamine to the drug "wanting" or loss of enjoyment that people with established stimulant dependence experience.

In contrast to subjective measures, the objective measure of eye blinks did not differ among the study conditions. This result is inconsistent with our previous work (Strakowski et al. 1996; Strakowski and Sax 1998). In our previous studies, subjects served as their own controls, so ratings of eye blinks, which were made directly without videotaping, may have been unintentionally biased by raters who observed subjects as they sequentially received both placebo and d-amphetamine, although the order of this administration was blinded. With the institution of videotaped eye-blink ratings, this risk of rater bias was minimized, which may account for the differences in the studies.

Alternatively, the current sample exhibited considerable variability in the eye-blink rates observed (as is apparent in the size of the standard errors in Figure 3)[FIG 3], which may have caused significant effects to be lost in noise.

In this study, women were more likely than men to exhibit differences in d-amphetamine response based on the number of previous d-amphetamine exposures. This observation is consistent with animal studies of repeated stimulant administration in which female animals are more likely to exhibit behavioral sensitization than males (Robinson and Becker 1986). In epidemiologic studies, the prevalence of stimulant abuse and dependence seems to be more common in men than women (Anthony and Helzer 1991; Substance Abuse and Mental Health Services Administration (SAMHSA) 1998); however, our results suggest that women are less likely to exhibit progressive responses to d-amphetamine. Perhaps the greater neuroadaptability of women to repeated stimulant doses (i.e., exhibiting either enhancement or tolerance to different drug effects) alters their risk for developing stimulant dependence. Sex differences in epidemiologic rates of drug dependence do not simply reflect sex differences in neurobiological responses to drug use; however, a variety of other social and environmental have an impact on these rates (e.g., sex differences in drug exposure; Anthony and Helzer 1991). Clearly, more studies are needed to study sex differences specifically in response to repeated stimulant exposure to clarify how these differences might contribute to sex differences in developing addiction.

As with any study involving human subjects, this study has potential limitations. First, differences between this study and others may reflect differences in subject acquisition or study environment. People available to volunteer for studies at different sites may come from different populations, so that results at any one location may not generalize to others. Similarly, it is possible that the sex differences observed in this study reflect differences between men and women in ascertainment biases associated with volunteering for this study. Second, the number of subjects is relatively small, particularly for specific sex-by-group interactions, which introduces a risk of type II error. However, in our previous within-subjects designs (Strakowski et al. 1996; Strakowski and Sax 1998), smaller number of subjects (n = 11) provided adequate power to detect significant repeated drug effects. Finally, unlike animal subjects, a complex interaction exists between measured drug effects and expected drug effects in human subjects that may have influenced the findings we observed (Mitchell et al. 1996). The subjects' ability to "guess" what they have received, coupled with their expectations of what d-amphetamine effects were, is likely to influence their subjective response to drug ingestion. Unfortunately, in the absence of specific measures of expected drug effects, we cannot analyze how this interaction influenced our results. Given the change in perceived d-amphetamine effects over repeated doses observed in these subjects, a study to explore further how the expectations of human subjects influence the subjective drug responses in a repeated administration design seems warranted.

In summary, we observed significant progressive increases in some subjective behavioral ratings following

repeated d-amphetamine administration, which may serve as a human model for behavioral sensitization. However, a decrease or tolerance to drug liking also seemed to occur, suggesting a separate process from these other behavioral ratings. A human model of behavioral sensitization could help unravel the neurobehavioral mechanisms that underlie the development of stimulant and other drug dependence, as well as potentially serve as a template to develop new treatments for drug addiction. This model may also have application in the study of psychiatric disorders, such as schizophrenia or bipolar disorder. We are hopeful that these results will encourage other investigators to extend and test this approach to such a model.

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