Pharmacology Biochemistry and Behavior, Vol. 66, No. 3, pp. 509–515, 2000

0091-3057/00/$–see front matter

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PII S0091-3057(00)00218-5

Acute Effects of *d*-Amphetamine During the Early and Late Follicular Phases of the Menstrual Cycle in Women

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Received 23 August 1999; Revised 10 November 1999; Accepted 28 November 1999

JUSTICE, A. J. H. AND H. de WIT. *Acute effects of* d-*amphetamine during the early and late follicular phases of the menstrual cycle in women*. PHARMACOL BIOCHEM BEHAV **66**(3) 509–515, 2000.—Recent preclinical evidence indicates that ovarian hormones, such as estrogen and progesterone, may influence the behavioral effects of psychoactive drugs by interacting directly with neurotransmitter systems in the central nervous system. However, few studies have examined the effects of ovarian hormones on subjective or behavioral responses to psychoactive drugs in humans. In the present study, we assessed the subjective and physiological effects of d-amphetamine during the early and late follicular phases of the menstrual cycle. Nineteen healthy, regularly-cycling women participated in four sessions receiving doses of d-amphetamine (AMPH; 15 mg oral) or placebo during the early and late follicular phases of two menstrual cycles. During the early follicular phase levels of both estrogen and progesterone are low, whereas during the late follicular phase estrogen levels are higher while progesterone remains low. Dependent measures included self-report questionnaires, physiological measures and plasma hormone levels. Most of the subjective and physiological effects of AMPH were not affected by menstrual cycle phase. However, subjects reported greater Unpleasant Stimulation after AMPH, and less Unpleasant Sedation, during the late follicular phase than during the early follicular phase. These results provide limited evidence that higher levels of estrogen during the late follicular phase alter the subjective effects of AMPH in normal, healthy women. © 2000 Elsevier Science Inc.

Estrogen Menstrual cycle *d*-Amphetamine Subjective effect

THERE is considerable evidence from preclinical studies suggesting that the behavioral and neurochemical effects of stimulant drugs, such as *d*-amphetamine (AMPH), vary across the estrous cycle, and are related to relative levels of estrogen and progesterone. For example, female rats exhibit more stereotypy (2) and rotational behavior (3), and release more dopamine (DA) [e.g., (2,4)] in response to AMPH when estrogen levels are high relative to progesterone levels. This enhancement of behavioral and neurochemical responses to AMPH may be mediated by interactions between estrogen and DA. Dopaminergic activity increases in response to exogenous administration of estradiol in rats. For example, in ovariectomized rats, estradiol increases dopamine synthesis (19,20), turnover and release [e.g., (4,5,8)], and DA receptor density (11,21). Estrogen also decreases monoamine oxidase activity thereby regulating the degradation of DA (16). These data suggest that estrogen may increase responses to AMPH by increasing the activity of the dopamine system.

Consistent with these preclinical findings, we recently reported that the subjective and behavioral effects of AMPH varied across the menstrual cycle, possibly related to relative levels of estrogen and progesterone (12). Subjects reported feeling more "high," "energetic and intellectually efficient," and "euphoric," and liking and wanting the drug more when AMPH was administered during the follicular phase, compared to the luteal phase. Further analyses of these data showed that subjects' responses to AMPH during the follicular phase were related to plasma levels of estrogen, in particular, when levels of estrogen were high relative to progesterone. These findings are consistent with preclinical findings suggesting that in the absence of progesterone, estrogen may enhance responses to stimulant drugs.

Results of another study from our laboratory using normal, cycling women tested during the early follicular phase showed that acute transdermal estradiol treatment, which raised plasma estradiol levels to about 10-fold the physiologic

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levels normally observed during the follicular phase, increased subjective ratings of pleasant stimulation after AMPH (13). Also, estradiol increased subjective ratings of pleasant stimulation when it was administered alone.

The finding that estradiol treatment increased ratings of stimulation is consistent with the results of our previous study comparing the effects of AMPH at the follicular and luteal phases of the cycle (12) and with a recent report comparing the subjective effects of smoked cocaine at different phases of the menstrual cycle in women. Sofuoglu et al. (22) found that cocaine produced greater increases in stimulation in women tested during the follicular phase compared to the luteal phase. The findings from both studies (12,22) that stimulant drugs produce greater stimulant effects when estrogen levels are high relative to progesterone suggests that there is a partial interaction between estradiol and the subjective effects of stimulant drugs. To further investigate the previously observed relationship between estradiol level and response to AMPH during the follicular phase (12), the present study was designed to compare directly the subjective and behavioral effects of AMPH administered early or late in the follicular phase. Based on our previous results as well as preclinical studies, we hypothesized that the effects of AMPH would be greater during the late follicular phase, when estrogen levels are high, than during the early follicular phase when they are very low.

METHOD

Design

Subjects participated in a within-subject study consisting of four laboratory sessions, conducted across two consecutive menstrual cycles. Two sessions were scheduled to occur during the early follicular and two during the late follicular phases of each subject's cycle. Subjects received *d*-amphetamine (15 mg) and placebo, in a quasi-random order so that they received drug and PL once at each phase. Drugs were administered under double-blind conditions. This dose of AMPH was chosen because it is known to produce modest, but reliable, subjective effects, thereby allowing us to detect phase-dependent increases or decreases in the magnitude of response (6). Subjective, behavioral, and physiological responses were assessed at regular intervals during the session. After completing all four sessions, subjects were debriefed and paid for their participation.

Subject Recruitment and Screening

Twenty women, aged 18–35, were recruited from the university and surrounding community via posters, advertisements in newspapers, and by word-of-mouth referrals. Initial eligibility was ascertained in a telephone interview. Eligible candidates reported to the laboratory to complete standardized self-report questionnaires including the Symptom Checklist-90 (7), and a health questionnaire containing items of general health and drug and alcohol use. Screening included a physical examination, an electrocardiogram, a semistructured psychiatric interview, and urine pregnancy tests. Exclusion criteria were: irregular menstrual cycles, menstrual cycles shorter than 25 days or longer than 35 days, amenorrhea, severe premenstrual syndrome diagnosed according to DSM IV criteria (1), or any menstrual cycle dysfunction, use of hormonal contraceptives, lactation, pregnancy or plans for pregnancy, and endocrine, medical, or Axis I (1) psychiatric or substance use disorders. The procedure was approved by the Institutional Review Board at the University of Chicago Hospital.

Before the study, subjects read and signed the consent form and any questions about it were answered. The consent form outlined the procedures to be followed, and listed the classes and possible effects of any drugs that subjects might receive. For blinding purposes, subjects were told that on any session they might receive a stimulant, tranquilizer, hormone, or placebo. They were instructed to abstain from alcohol and other drugs before the sessions, and this was verified using breath alcohol levels (BAL) and urine toxicology tests. BALs were determined prior to each session using an Intoximeter Breathalyzer. No BAL reading was positive. Urine samples were obtained prior to each session and screened for pregnancy. In addition, one of the urine samples was randomly selected for a urine toxicology screen to verify the non-use of stimulants, barbiturates, opioids, and benzodiazepines. No urine toxicology screen was positive. Subjects agreed not to take any other drugs for 12 h before and 6 h following each session.

Laboratory Environment

Sessions were conducted in comfortably furnished rooms in the Human Behavioral Pharmacology Laboratory (HBPL) in the Department of Psychiatry. Subjects were tested individually and were allowed to bring in their own recreational materials.

Procedure

Subjects participated in a total of four, 4.5-h sessions over the course of two menstrual cycles in the HBPL. During each cycle, one session was conducted during the early follicular phase, 2–7 days after the onset of menstruation, and one during the late follicular phase, 8–13 days after the onset of menstruation. During the early follicular phase sessions levels of estrogen are low [i.e., estrogen around 50 pg/ml; (10)], whereas during late follicular phase sessions levels of estrogen are rising [up to 400 pg/ml; (10)]. Progesterone levels are very low throughout the follicular phase. When a session was missed due to illness or scheduling problems, subjects made up the appropriate session in their next cycle. Half of the subjects started during the early follicular phase, and the other half started during the late follicular phase, and half received PL first, while the other half received AMPH first.

Session Protocol

On each session, subjects reported to the Clinical Research Center (CRC) at 0730 h, after fasting overnight. Upon arrival they provided a blood sample for estradiol and progesterone assays, and urine samples for pregnancy and toxicology tests. Blood samples were centrifuged, and the serum was frozen at −70°C until the hormone assays were conducted. Immediately after the blood and urine samples were obtained and a negative pregnancy test was confirmed, subjects reported to the HBPL where they stayed for the remainder of the session. There, subjects completed baseline questionnaires to assess their mood (see below) and their heart rate, blood pressure and temperature were recorded. At 0800 h they ingested two capsules containing AMPH (total = 15 mg) or placebo with 100 ml water. AMPH and placebo capsules were opaque, colored gelatin capsules (size 00) and were identical in appearance. AMPH capsules were packed with dextrose filler; placebo capsules contained only dextrose.

Subjects received drug and placebo each during the early and late follicular phases of their menstrual cycles. Drug administrations were double blind. After taking the capsules, subjects completed mood questionnaires, and vital signs were recorded at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, and 4 h after ingesting the capsules. Subjects were free to relax between measures, and they left the laboratory shortly after 1200 h.

Dependent Measures

Subjective effects of AMPH were assessed with the Profile of Mood States [POMS; (18)], the Addiction Research Center Inventory [ARCI; (17)], and two visual analog questionnaires, the Stimulant Sedative Questionnaire [SSQ; (14)] and the Drug Effects Questionnaire (DEQ). The POMS consists of 72 adjectives commonly used to describe momentary mood state. Subjects indicate how they feel at that moment in relation to each of the adjectives on a five-point scale ranging from "not at all" [0] to "extremely" [4]. The 49-item ARCI is a true-false questionnaire with five empirically derived scales: A (Amphetamine-like, stimulant effects), BG (Benzedrine Group, energy and intellectual efficiency), MBG (Morphine–Benzedrine Group, euphoric effects), LSD (Lysergic Acid Diethylamide, dysphoric effects, somatic complaints), and PCAG (Pentobarbital–Chlorpromazine–Alcohol Group, sedative effects). The SSQ is a locally developed 22-item questionnaire with four factor-analyzed measures consisting of clusters of adjectives associated with visual analogue scales: Pleasant Stimulation (PStim), Unpleasant Stimulation (UStim), Pleasant Sedation (PSed) and Unpleasant Sedation (USed). PStim consists of five adjectives: "alert," "focused," "outgoing," "energetic," and "lively". UStim consists of six adjectives: "restless," "anxious," "jittery," "on edge," "uneasy," and "nervous;" PSed consists of five adjectives: "calm," "relaxed," "peaceful," "contented," and "mellow;" and USed consists of six adjectives: "tired," "sluggish," "worn out," "drowsy." "slow," and "heavy." The SSQ was administered hourly as opposed to the other measures, which were measured at half-hour intervals. The DEQ assessed the subjective states "Feel Drug," "Feel High," "Like Drug," and "Want More," also on visual analogue scales. The primary dependent measures were the PStim scale of the SSQ, the A (AMPH-like effects), and BG (Energy and Intellectual Efficiency) scales of the ARCI and the "Feel Drug" scale of the DEQ. With the exception of PStim, which is relatively new, these measures have been shown to be sensitive to the effects of a variety of psychoactive drugs, including stimulants (9). PStim has been shown to be sensitive to the effects of stimulant drugs (13).

Plasma samples were assayed for estradiol and progesterone at the University of Chicago Endocrinology Laboratory. Plasma estradiol levels were measured using the IMx (Abbott Laboratories) Estradiol assay, which is based on the Microparticle Enzyme Immunoassay technology. It has a sensitivity of 25 pg/ml, an interassay coefficient of variation of less than 10%, and a very low cross-sensitivity with other compounds. Plasma progesterone levels were measured using the Coat-a-Count Progesterone procedure (Diagnostic Products Corporation). This procedure has a sensitivity of 0.02 ng/ml, low and uniform coefficients of variation in retests, and a low crossreactivity to other compounds.

Data Analysis

To determine whether the responses to AMPH were different in the early and late follicular phases three-way repeated-measures ANOVAs were conducted on each dependent measure with within-subjects factors of phase (early or late), drug (AMPH or PL), and time (precapsule and repeated measures within sessions). To minimize the influence of variability between subjects prior to capsule administration, physiological data and scores on ARCI, POMS, and SSQ measures were calculated as change from baseline (i.e., precapsule score was subtracted from each subsequent timepoint). For the DEQ, which was not administered prior to capsule administration, only raw scores were used. Due to the variability of estrogen levels, supplemental analyses were conducted using only the data from subjects whose estrogen levels were within the expected range during the early and late follicular phases. For all analyses, *F*-values were considered significant at $p < 0.05$. Fisher-Hayter post hoc comparisons were conducted when significant phase by drug by time interactions were observed. All analyses were conducted with SPSS for Macintosh v. 6.1.1.

RESULTS

Subject Characteristics

Nineteen women completed the study and provided usable data. One subject did not complete the study due to scheduling problems. Their mean age was 24 years (SD 5.0), mean height 164.8 cm (SD 6.6), mean weight 63.1 kg (SD 7.4). Twelve subjects were Caucasian, three were African American , three were Asian, and one was Hispanic. They reported consuming a mean of two alcoholic drinks and 3.7 caffeinated beverages each week. Five subjects reported some cigarette use, smoking a mean of 2.9 cigarettes a day (SD 2.8). No subjects smoked more than five cigarettes a day. They reported minimal use of other recreational drugs. Subjects had regular menstrual cycles, with an average length of 27.8 days (range 25–32 days), and an intercycle variability of 2 or 3 days at most.

Hormone Levels

Table 1 shows the mean, standard deviation, minimum, and maximum levels of estradiol during the AMPH and placebo sessions at the early and late follicular phases of the cycle. All plasma samples were taken prior to drug administration. Estradiol levels were significantly greater during the late follicular phase than during the early follicular phase, $F(1, 18) = 40.08$, $p < 0.001$. Figure 1 shows the estradiol levels for the 19 individual subjects on both the AMPH and placebo sessions during the early and late follicular phases expressed

TABLE 1

PLASMA LEVELS OF ESTRADIOL (E_2) DETERMINED FROM PRECAPSULE PLASMA SAMPLES ON PLACEBO AND AMPH SESSIONS

	Early Follicular		Late Follicular	
	Preplacebo	Pre-AMPH	Preplacebo	Pre-AMPH
	E_2 (pg/ml) n = 19	E_2 (pg/ml) n = 19	E_2 (pg/ml) n = 19	E_2 (pg/ml) n = 19
Mean	55.74	57.16	146.21	175.73
SD	33.53	29.24	88.91	108.94
Min	22.00	17.00	27.00	40.00
Max	149.00	132.00	316.00	365.00

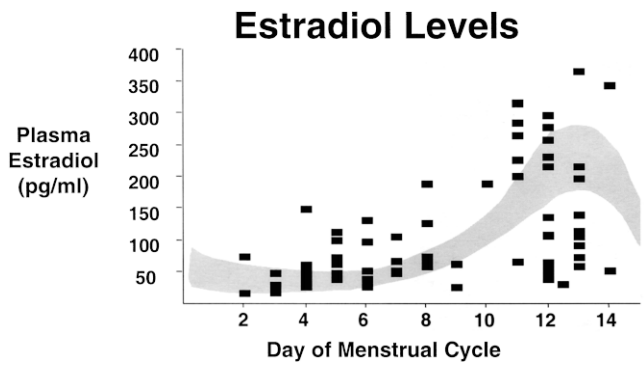

FIG. 1. Plasma levels of estradiol plotted as a function of the number of days past the onset of menses. Each subject ($n = 19$) was tested twide during each phase, so the total number of observations for each phase is 38. Shaded areas show expected values of estradiol (10).

as a function of days from the onset of menstruation. Expected values are also shown (10). It is immediately apparent that there was a great deal of variability in estradiol levels, particularly during the late follicular phase. However, even though some of the levels during the late follicular phase were lower than expected, most subjects had higher estradiol levels during the late follicular phase than the early follicular. For example, one subject had estradiol levels during the early follicular phase on placebo and AMPH sessions of 28 and 19 pg/ml, respectively; and her estradiol levels during the late follicular phase on placebo and AMPH sessions were 59 and 53 pg/ml. Thus, although the estradiol levels obtained by this subject are lower than the population average, they changed in the expected manner across the cycle.

It is notable that this degree of individual variation in hormone levels across subjects has been reported by other investigators as well (23). However, because the hypothesis of the study involved interactions between estrogen levels and drug responses, we also conducted secondary analyses using the data only from subjects whose estradiol levels reached the expected levels (see below). As expected, progesterone levels were low at both stages of the follicular phase (mean 1.3 ng/ml, SD 1.9 ng/ml).

Effects of AMPH

Regardless of menstrual cycle phase, there were several significant drug by time interactions. AMPH increased systolic blood pressure, $F(7, 126) = 4.82$, $p < 0.001$, diastolic blood pressure, $F(7, 126) = 3.93$, $p < 0.001$, and heart rate, $F(7, 126) = 2.14$, $p < 0.05$, and produced its prototypic subjective effects such as increased ratings of "feel drug" [DEQ; $F(7, 126) = 4.30$, $p < 0.001$], AMPH-like effects [ARCI A scale; $F(7, 126) = 6.42$, $p < 0.001$], euphoria [ARCI MBG scale; $F(7, 126) = 7.63$, $p < 0.001$], pleasant stimulation [SSQ; $F(3, 54) = 4.99$, $p < 0.01$], vigor [POMS; $F(7, 126) = 5.32$, $p < 0.001$], and friendliness [POMS; $F(7, 126) = 3.06$, $p < 0.01$]. These results are summarized in Fig. 2 and Table 2. Figure 2 shows subjective ratings of "feel drug" (VAS) and systolic blood pressure after AMPH.

Effects of Phase

There were no main effects of menstrual cycle phase on any subjective, behavioral, or physiological measure.

Effects of AMPH + Phase

Ratings of UStim after AMPH decreased in the early follicular phase, relative to placebo, but increased in the late follicular phase [Fig 3; significant phase × drug interaction, $F(1, 18) = 6.43$, $p < 0.02$]. Ratings of "like drug" after AMPH increased slightly more in late follicular phase than the early follicular phase [Fig 3; significant phase × drug × time interaction, $F(7, 126) = 3.77$, $p < 0.001$]. On the USed scale, a significant phase × drug × time interaction was observed, $F(3, 54) = 6.81$, $p < 0.001$]. Figure 4 shows that AMPH decreased ratings of USed, relative to placebo, in both the early and late follicular phases, but AMPH decreased ratings of USed more during the early follicular phase than the late follicular phase. When the three-way ANOVAs for the subjective effects were recalculated using only those subjects whose estrogen levels were within the expected range during the early and late follicular phases, the same pattern of results were obtained.

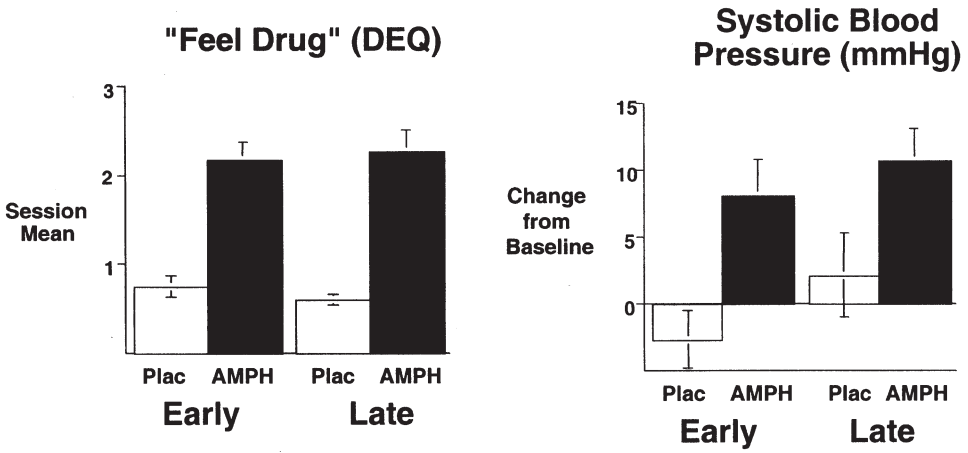

FIG. 2. Mean (SEM) for subjective ratings of "feel drug" (DEQ; left panel) and systolic blood pressure (right panel) during the early and late follicular phases. Filled bars represent data from AMPH sessions. Open bars represent data from placebo sessions. The maximum score on the DEQ is 10.

TABLE 2

SUMMARY OF SIGNIFICANT *F*-VALUES FOR MAIN EFFECTS OF AMPH AND TIME, INTERACTIONS BETWEEN AMPH AND TIME, MENSTRUAL CYCLE PHASE AND AMPH, PHASE AND TIME, AND INTERACTIONS BETWEEN PHASE, AMPH AND TIME

	AMPH	Time	AMPH × Time	Phase × AMPH	Phase × Time	Phase × AMPH Time
SSQ						
Pleasant stimulation	55.04‡	6.92‡	4.99†			
Unpleasant stimulation		3.97†		6.43*		
Unpleasant sedation (decreased)	4.82*		6.37‡		4.13†	6.81‡
DEQ						
Feel drug	15.92‡	11.76‡	4.30‡			
Like drug	7.26†		4.94‡			3.77‡
Feel high	10.00†	7.09‡	4.85‡			
Want more	12.43†	3.63‡	4.87‡			
POMS						
Friendliness	8.19†		3.06†‡			
Vigor	35.93‡	2.2*	5.32†‡			
Fatigue (decreased)	8.22†	6.83‡	4.91†‡			
Confusion (decreased)		3.04†				
ARCI						
Energy (BG)	13.6†	4.18‡				
AMPH-like (A)	17.38‡	5.2‡	6.42‡			
Euphoria (MBG)	23.35‡	4.5‡	7.63‡			
Sedation (PCAG; decreased)	13.77†	3.22†	6.16‡			
Physiological						
Systolic BP	24.05‡	9.65‡	4.82‡			
Diastolic BP	16.10‡	7.13‡	3.93‡			
Heart rate		2.72†	2.14*			

There were no main effects for menstrual cycle alone.
*$p \leq 0.05$; †$p \leq 0.01$; ‡$p \leq 0.001$.

DISCUSSION

Contrary to expectation, the present study demonstrated that the majority of the subjective, behavioral and physiological effects of AMPH did not vary across the early and late follicular phases of the menstrual cycle in normal, cycling women even though levels of estrogen were significantly higher during the late follicular phase. Nevertheless, some differences in response to AMPH were observed between the early and late follicular phases. For example, subjects reported more unpleasant stimulation (anxiety, restlessness) during the late follicular phase than the early follicular phase. Subjects also reported that AMPH decreased unpleasant sedation (tired, sluggish) more during the early follicular phase than the late follicular phase.

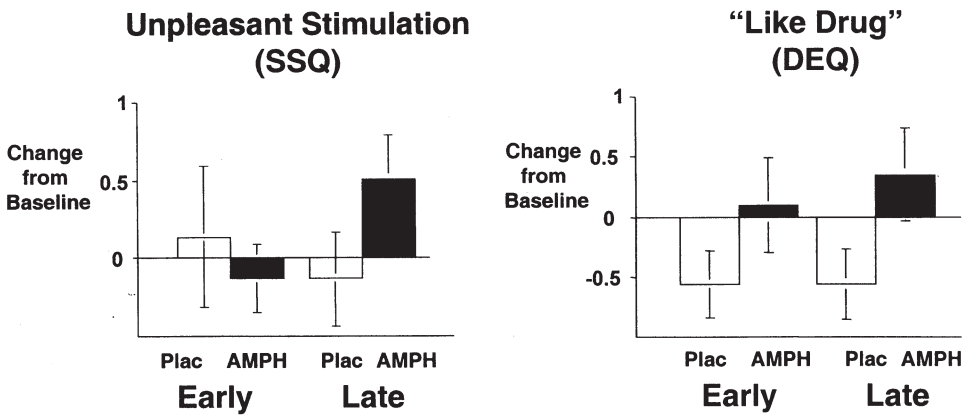

FIG. 3. Mean (SEM) subjective ratings of unpleasant stimulation (SSQ UStim; left panel) and "like drug" (DEQ; right panel) during the early and late follicular phases. Filled bars represent data from AMPH sessions. Open bars represent data from placebo sessions. The maximum score on the SSQ and DEQ is 10.

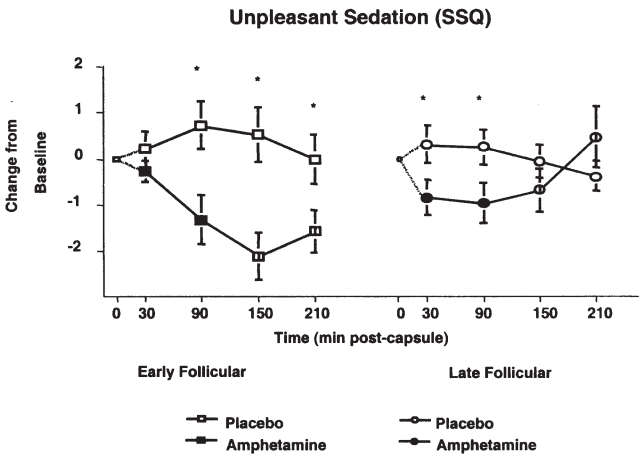

FIG. 4. Mean (SEM) subjective ratings of unpleasant sedation (SSQ USed) during the early and late follicular phases. Filled symbols represent data from AMPH sessions. Open symbols represent data from placebo sessions. A significant drug × phase × time interaction was observed on USed. Fisher-Hayter post hoc tests were conducted. Asterisks indicate which points are different from placebo (Fisher-Hayter post hoc, $p < 0.01$); partially filled symbols indicate which points are significantly different between phases. The maximum score on the SSQ is 10.

The finding that AMPH increased ratings of unpleasant stimulation during the late follicular phase is not consistent with results from our previous studies suggesting that higher levels of estrogen (in the presence of low progesterone levels) increase ratings on scales indicative of the pleasantly stimulating and euphoric effects of AMPH. One explanation for these findings is that estrogen acted additively with AMPH and instead of simply increasing the pleasant effects linearly with dose, it increased the drug's effects beyond the level that is considered pleasant. That is, it is possible that past a certain point the pleasant effects (arousal) of AMPH become unpleasant (anxiety). However, this interpretation is inconsistent with our previous finding (13) that acute estradiol pretreatment, which resulted in plasma estradiol levels 10 times higher than those achieved during the late follicular phase, increased ratings of pleasant stimulation after AMPH, and did not result in unpleasant effects. Moreover, subjects in the present study reported no other negative mood states such as anxiety. In the first Justice and de Wit study (1999), we reported that the effects of AMPH were greater during the late follicular phase than during the early follicular phase, coinciding respectively with higher, and lower levels of estradiol Although the present study was designed explicitly to follow up on this finding, the results did not support the original finding. This raises the possibility that the original finding was a chance finding. Although this possibility must be considered, the original finding was consistent with the preclinical evidence cited above, whereas the present findings are not. This issue could only be resolved by testing additional subjects.

There were several limitations to this study. First, only a single, moderate dose of AMPH was tested. This dose of AMPH was chosen because we expected to observe an increase in subjective responses during the late follicular phase. It is possible that estrogen–AMPH interactions would emerge if lower, or even higher, doses of AMPH were used. Another limitation to this study is that we did not measure plasma AMPH levels, leaving the possibility that estradiol altered the pharmacokinetic profile of AMPH. Lukas et al. (15) recently reported that women achieved higher plasma levels of cocaine after intranasal administration during the follicular phase compared to the luteal phase, and attributed this difference to alterations in cocaine pharmacokinetics. However, in the present study, the pattern of early vs late differences were not indicative of a pharmacokinetic effect. Indeed, the majority of the effects of AMPH were similar during the early and late follicular phase, making it unlikely that the interaction was related to differences in absorption, distribution, or clearance across the phases.

In summary, it is not clear why interactions between estradiol level and responses to amphetamine were not observed in the present study. Studies with laboratory animals [e.g., (3)] clearly suggest that estrogen enhances the behavioral effects of stimulant drugs, and our previous studies (12,13) suggested that a similar interaction might occur between estrogen and subjective responses to amphetamine in humans. In the present study, amphetamine produced its prototypic subjective effects of increased feelings of arousal and well being, but there was little evidence that these effects were greater in the presence of higher circulating levels of estradiol. It is possible that the interaction between estrogen and stimulant drugs is relatively modest, and difficult to detect with the level of variability typically seen with measures of subjective responses. Thus, it may be that larger numbers of subjects are needed to reliably demonstrate this interaction. Alternatively, it may be that the behavioral responses studied in laboratory animals are not homologous with the subjective effects measured in human volunteers. Whether or not a larger N would reveal a significant result, however, the present findings suggest that whatever interactions do occur, are not robust, and therefore, may not be clinically relevant in womens' responses to this class of drug.

ACKNOWLEDGEMENTS

This work was supported by grants from the NIH (R01 DA02812 and M01 RR00055). The authors thank Christopher O'Connor, Aaron York, Paul Meyer, and Angella Charnot for excellent technical assistance.

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