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Differential subjective effects of D-amphetamine by gender, hormone levels and menstrual cycle phase

Tara L. White*, Angela J.H. Justice, Harriet de Wit

Department of Psychiatry MC3077, University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637, USA

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Abstract

Estrogen and progesterone interact with monoamines in ways that suggest the potential modulation of responses to psychoactive drugs by endogenous steroids, both between menstrual phases and between the sexes. The present study assessed the subjective and physiological effects of a single dose of D-amphetamine (AMPH; 15 mg oral) in healthy, normally cycling women ($n=13$), who received amphetamine and placebo (PL) during both the follicular and luteal phases of a single menstrual cycle, and in healthy men ($n=7$). Females reported greater amphetamine-induced subjective stimulation [Addiction Research Center Inventory (ARCI)-A, ARCI-MBG; Drug Effects Questionnaire (DEQ) Feel Drug, Feel High, Want More] during the follicular phase than the luteal phase. Within the follicular phase, the magnitude of individuals' AMPH-induced stimulation was positively associated with baseline (predrug) salivary estradiol [$r=+.55-.78$; Profile of Mood States (POMS) Vigor, Positive Mood, Elation], and negatively associated with salivary progesterone [$r=-.66-.68$; POMS Friendliness; Subjective States Questionnaire (SSQ) Pleasant Sedation]. Sex differences also emerged. Males reported feeling greater AMPH-induced stimulation (ARCI-A, ARCI-MBG; DEQ Feel Drug, Want More) than females in the luteal phase. Thus, higher levels of estrogen and lower levels of progesterone are associated with greater subjective stimulation after AMPH in women, and these hormonal influences contribute to sex differences in amphetamine responding.

Keywords: Menstrual cycle phase; D-Amphetamine; Stimulants; Dopamine; Estrogen; Estradiol; Progesterone; Subjective effects; Individual differences; Sex differences; Gender; Human

1. Introduction

The ovarian hormones estrogen and progesterone appear to have direct and opposing actions on brain monoamine (serotonin, dopamine, norepinephrine) systems, which suggests that monoaminergic drugs, such as amphetamine, may produce differential effects in men and women and in women at different phases of the menstrual cycle. Basal and drug-elicited monoamine activity have been investigated in relation to both endogenous and exogenous sources of estrogen and progesterone. In rats, when endogenous estradiol is high (during estrus and proestrus), dopamine turnover is high (proestrus; Shimizu and Bray, 1993), and extracellular concentrations of dopamine in the striatum and accumbens are high and stable (Dluzen and Ramirez, 1985; Xiao and Becker, 1994). Exogenous administration of estradiol increases turnover of dopamine in the accumbens (rat; Shimizu and Bray, 1993), increases receptor density in the striatum (rat; Hruska and Silbergeld, 1980; Hruska et al., 1982) and increases concentrations of dopamine in the ventromedial amygdala (mountain spiny lizards; Woodley et al., 2000; reviewed by Becker, 1999). In contrast, progesterone appears to down-regulate dopamine systems. Exogenous administration of progesterone in rats decreases dopamine turnover in striatum (Fernandez-Ruiz et al., 1990) and reduces estradiol-induced dopamine turnover in the accumbens (Shimizu and Bray, 1993), limbic regions and striatum (Fernandez-Ruiz et al., 1990). Thus, there is considerable evidence in laboratory animals that estrogen and progesterone influence monoamine function in the brain.

These effects of ovarian steroids on monoamine function are likely to have behavioral consequences, including alterations in the effects of stimulant drugs. Evidence from animal studies indicates that exogenous estradiol, in par-

* Corresponding author. Tel.: +1-773-702-0084; fax: +1-773-834-7698.

E-mail address: twhite@yoda.bsd.uchicago.edu (T.L. White).

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ticular, heightens the behavioral and dopamine responses to amphetamine (Becker and Cha, 1989; Becker and Rudick, 1999; Becker et al., 1982; for a review, see Becker, 1999). For instance, 4 days of estradiol treatment in ovariectomized rats increased the effects of amphetamine on both striatal dopamine levels and stereotyped behavior (Becker and Beer, 1986). The effects of estradiol on behavioral responses to stimulant drugs are thought to reflect the effects of estradiol on neuronal excitability (Becker, 1999), dopamine synthesis (see Pasqualini et al., 1995, 1996; Woodley et al., 2000) and cytosolic dopamine availability (Kuczenski, 1983). In contrast, the effects of progesterone on neurochemical and behavioral responses to stimulants are complex. Progesterone *increases* amphetamine-induced dopamine release when it is administered intermittently (Dluzen and Ramirez, 1987, 1990), but it *inhibits* dopamine release when it is administered in a continuous infusion (Dluzen and Ramirez, 1987). Progesterone has been found to significantly dampen the facilitation of stimulant effects by estradiol in some studies (cocaine; Quinones-Jenab et al., 2000) but not in others (cocaine: Perrotti et al., 2001; Sell et al., 2000; amphetamine: Becker and Rudick, 1999). Thus, while estrogen has consistently been found to increase responses to stimulant drugs in laboratory animals, the effects of progesterone are variable, depending on the specific dose and dosing regimens used.

In humans, variation in the levels of estradiol and progesterone also appears to affect responses to stimulant drugs. Across menstrual cycle phases and between men and women, D-amphetamine (AMPH) (Justice and de Wit, 1999) and cocaine (Sofuoglu et al., 1999; Lukas et al., 1996) appear to exert greater euphoric and stimulant effects during the follicular phase of the menstrual cycle, when estradiol is high relative to progesterone, than during the luteal phase, when both estradiol and progesterone are high. Amphetamine produces smaller increases in ratings of "high", euphoria, energy and intellectual efficiency when it is administered in the luteal, compared to the follicular, phase (Justice and de Wit, 1999) and cocaine produces a smaller increase in "high" when it is administered in the luteal, compared to the follicular, phase (Sofuoglu et al., 1999; Lukas et al., 1996). Further, women's responses to cocaine during the luteal phase responses are less strong than responses to cocaine in men (Sofuoglu et al., 1999). Justice and de Wit (2000b) examined effects of AMPH during the early versus late follicular phases of the cycle, which are associated with low and higher estradiol levels, respectively. The effects of amphetamine did not differ in the early versus later follicular phase, suggesting that estradiol levels alone do not explain the variability in response to stimulant drugs. Several lines of evidence suggest that progesterone has mood-altering effects that may interact with responses to stimulant drugs. For example, certain progesterone metabolites are known to be potent ligands at the $GABA_a$ receptor and produce sedative effects in animals (Majewska, 1992). In humans, exogenous administration of progesterone produces negative mood effects, including reductions in ratings of vigor and friendliness (Freeman et al., 1993; de Wit et al., 2001).

The present study was designed to investigate further the effects of menstrual cycle, gender and ovarian hormone levels on responses to AMPH in healthy male and female volunteers. The goals of this study were threefold: (1) to determine whether responses to amphetamine vary as a function of menstrual cycle phase in normally cycling women; (2) to determine whether differences in responses to amphetamine exist between males and females; and (3) to determine whether responses to AMPH in women are related to circulating endogenous levels of progesterone and estradiol.

2. Methods

2.1. Design

Oral doses of AMPH (15 mg) and placebo (PL) were investigated in healthy male and female volunteers in a double-blind, randomized, crossover design. Female participants took part in four laboratory sessions, conducted across one menstrual cycle. Two sessions were scheduled during the follicular phase and two sessions were scheduled during the luteal phase of each participant's cycle, so that the women received AMPH (15 mg) and PL in random order in *each* phase, at least 48 h apart. Male participants participated in two sessions conducted no more than 3 weeks apart, in which they received either AMPH (15 mg) or PL in random order. The 15-mg dose of AMPH was chosen as it produces reliable modest subjective effects, which would permit detection of either increases or decreases in the magnitude of responses across the phases. Subjective, behavioral and physiological responses were assessed at 30-min intervals during the sessions.

2.2. Participant recruitment and screening

Sixteen women and seven men aged 18–35 were recruited from the university and surrounding community via posters and newspaper advertisements. Initial eligibility was ascertained in a telephone interview. Eligible candidates reported to the laboratory to complete standardized self-report questionnaires including the Symptom Checklist (SCL-90; Derogatis, 1983) and a health questionnaire containing items concerning general health and drug and alcohol use. Screening procedures involved a physical examination, an electrocardiogram, a semistructured psychiatric interview and urine pregnancy tests. Exclusion criteria were existence of a Major Axis I psychiatric disorder or history of psychosis, serious medical condition, history of cardiac or liver disease, high blood pressure, body mass index >25, history of drug or alcohol depend-

ence (as determined in the diagnostic interview or a Michigan Alcoholism Screening Test score over 4), total abstention from drugs and alcohol, cigarette use of >10 cigarettes/day and night shift work. Additional exclusion criteria for women included current or planned pregnancy, lactation, recent history of amenorrhea, premenstrual syndrome or menstrual cycle dysfunction and use of hormonal contraceptives. The procedure was approved by the Institutional Review Board of the University of Chicago Hospital.

Participants read the consent form and were introduced to the protocol during the initial screening interview and again during the prestudy orientation session. The consent form outlined the procedures to be followed and listed the classes and possible effects of any drugs that participants might receive. For blinding purposes, participants were told that on any session they might receive a stimulant, tranquilizer, PL or alcohol. Breath alcohol level (BAL) was determined prior to each session using an Intoximeter Breathalyzer. All BAL readings were negative. Participants agreed not to take any other drugs, other than their usual amounts of caffeine and/or nicotine, for 12 h before and 6 h following each session. Drug compliance was verified through urine toxicology tests prior to each session. Participants were not permitted to consume caffeine or nicotine during the sessions.

2.2.1. Follicular phase sessions

Follicular phase sessions were scheduled 2–10 days after the first day of menstruation. To schedule the sessions, participants telephoned the researcher on the first day of menstruation. The two sessions were conducted at least 48 h apart. Menstrual cycle phase was verified by salivary levels of estradiol and progesterone, which are good indicators of ovarian function (Lu et al., 1999; Bourque et al., 1986). During this portion of the follicular phase, progesterone levels remain low, while estrogen levels are initially low and then begin to rise. The 2–10-day range of days for testing during the follicular phase provided for some variation in estrogen levels across participants. This range of variation allowed us to examine the correlation between estrogen levels and responses to AMPH.

2.2.2. Luteal phase sessions

Luteal phase sessions were scheduled 6–10 days after ovulation, as detected by the surge in luteinizing hormone (LH) in urine. To identify the day of ovulation, female participants were given kits to measure their urinary LH at home everyday at 6 p.m., beginning 9–15 days after onset of menses, depending on the length of their cycle. They telephoned the laboratory to schedule their two luteal sessions within 6–10 days of the LH surge, at least 48 h apart. During this period of the cycle, plasma levels of estradiol are at a moderate level (140 pg/ml), whereas progesterone levels are very high (between 7.5 and 14.00 ng/ml; Griffin and Ojeda, 1996).

2.3. Laboratory environment

This study was conducted in a recreational laboratory environment that consisted of testing rooms furnished with couches and upholstered chairs, wall decorations, incandescent lighting, wall art, tables with magazines and board games, television, VCR and a choice of movies. Participants were tested individually and were allowed to bring their own recreational materials.

2.4. Session protocol

Female subjects participated in four sessions, two during the follicular phase (Days 2–10) and two during the luteal phase (6–10 days post LH surge). Male subjects participated in two sessions scheduled no more than 3 weeks apart. On each session, participants reported to the HBPL at 7:30 a.m., after fasting overnight. Upon arrival, they provided a saliva sample for hormone assays and urine samples for toxicology tests. Saliva samples were frozen at -30 °C until assay for estradiol and progesterone (females) or estradiol alone (males). After the saliva and urine samples were obtained and a negative pregnancy test was confirmed for female participants, participants completed baseline questionnaires to assess their mood and their heart rate and blood pressure were recorded. At 8:00 a.m., they ingested a capsule containing either AMPH (15 mg) or PL with 100 ml water. The order of administration was double-blind and randomly assigned. After ingesting the capsules, participants repeated the mood and performance tests and vital signs were recorded at every half hour for a 4.5-h period. Participants left the laboratory shortly after 12:30 p.m.

2.5. Dependent measures

The primary measures were the measures of subjective state as measured by an experimental version of the Profile of Mood States (POMS; McNair et al., 1971), the Addiction Research Center Inventory (ARCI; Martin et al., 1971) and two visual analog questionnaires concerning an adjective checklist and a Drug Effects Questionnaire (DEQ). The POMS consists of 72 adjectives commonly used to describe momentary mood states. Participants 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 (AMPH-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) (Martin et al., 1971). The visual analogue adjective checklist [Subjective States Questionnaire (SSQ)] is a locally developed 22-item questionnaire consisting of a series of 10-cm lines, labeled from

"not at all" to "extremely", on which participants place a vertical tick to mark the magnitude of their current mood or state. This consists of four factor-analyzed measures: Pleasant Stimulation (PStim, consisting of adjectives "alert", "focused", "outgoing", "energetic", and "lively"), Unpleasant Stimulation (UStim, consisting of adjectives "restless", "anxious", "jittery", "on edge", "uneasy", and "nervous"), Pleasant Sedation (PSed, consisting of adjectives "calm", "relaxed", "peaceful", "contented", and "mellow") and Unpleasant Sedation (USed, consisting of adjectives "tired", "sluggish", "worn out", "drowsy", "slow", and "heavy"). The DEQ is a locally developed visual analogue questionnaire that assesses the extent to which participants experience four subjective states: "Feel Drug", "Feel High", "Like Drug" and "Want More". Each of these measures is sensitive to the effects of a variety of psychoactive drugs, including stimulants (Fischman and Foltin, 1991; Justice and de Wit, 2000a,b).

Salivary estradiol and progesterone levels were determined in duplicate through Salimetrics LLC Testing Services (State College, PA) from saliva samples obtained using a passive drool technique (see Shirtcliff et al., 2000) prior to capsule ingestion on each session. Samples were stored at −30 °C. Estradiol levels were determined using radioimmunoassay, a procedure with a sensitivity of 0.25 pg/ml, a working range of 0.375–7.5 pg/ml, an interassay coefficient of variation (CV) of 9.0% and an intraassay CV of 6.45% (Salimetrics LLC, unpublished-a; Shirtcliff et al., 2000). The passive drool technique was adopted to avoid the assay confounds that characterize alternative cotton-based and gum-enhanced salivary steroid samples (see Shirtcliff et al., 2000, 2001). The clear saliva samples obtained permit noninvasive, repeated sampling of the biologically active, unbound fraction of these steroids, which enter saliva through passive diffusion in concentrations unaffected by changes in salivary flow rate (Vining et al., 1983). The salivary concentrations represent approximately 0.2–8% of serum estradiol (Lu et al., 1999) and 1–2% of serum progesterone (Bolaji, 1994; Lu et al., 1999). Salivary estradiol obtained through expectorated saliva correlates with serum and blood-spot estradiol on the order of r=.6–.72 (Shirtcliff et al., 2000) or higher (.76–.89; reviewed by Lu et al., 1999), though these associations may be stronger in some individuals than in others (Lu et al., 1999). Progesterone levels were determined through enzyme immunoassay (Salimetrics LLC), with a sensitivity of 10 pg/ml, a working range of 10.2–1000 pg/ml and an inter- and intraassay CV of 6.9% and 2.3%, respectively (Salimetrics LLC, unpublished-b). The current progesterone assay correlates with serum progesterone approximately r=.98 (r=.98, Salimetrics LLC, 2001, Assay Kits; r=.987, Bolaji, 1994), though this estimate may be somewhat high (r's can range from .75 to .93; see Lu et al., 1999). It must be noted, however, that plasma measures may provide more reliable estimates of ovarian hormones than salivary measures, as salivary estradiol measurement can underestimate serum–behavior correlations (Shirtcliff et al., 2000), and accurate salivary progesterone measurement requires careful use of non-cotton-based methods (Shirtcliff et al., 2001).

2.6. Data analysis

Three sets of analyses were conducted. (1) To determine whether responses to amphetamine and PL differ between the follicular and luteal phases of the menstrual cycle, repeated-measures univariate ANOVAs were conducted on each dependent measure for female participants' four experimental sessions. Within-subjects independent factors of Phase (follicular or luteal), Drug (AMPH or PL) and Time (baseline through 4.5 h post capsule administration) were entered into the analysis. Contributions of ovarian hormones were assessed through repeated-measures ANCOVAs to determine whether menstrual phase effects were mediated by salivary levels of estradiol and progesterone. (2) To determine whether responses to AMPH differed in males and females by menstrual phase, repeated-measures ANOVAs were conducted on each dependent measure by separately comparing the men's data with women's follicular and luteal responses. The between-subjects factor of Gender (male or female) and the within-subjects factors Drug (AMPH or PL) and Time (baseline through 4.5 h post capsule administration) were entered into this second set of analyses. (3) To determine the influence of endogenous hormones on amphetamine responding, peak change scores (from precapsule to the largest positive or negative value post capsule administration) were calculated for each dependent measure on the follicular and luteal AMPH sessions of female participants. Salivary estradiol and progesterone levels were correlated with peak change scores induced by amphetamine on each dependent measure. For all analyses, F values were considered significant at $P<.05$, and the source of the interactions was determined through Fisher's least significant difference (LSD) comparisons. Analyses were conducted using Statistica Version 5.5 and SPSS Version 10.0.

3. Results

3.1. Participants

Thirteen women and seven men completed the study. Data from one female participant were excluded based on estradiol and progesterone data, which indicated that this subject was tested only during the luteal phase. Male and female participants did not differ in age (females: 26.3 ± 5.1 years, males: 22.7 ± 3.7 years), height (females: 1.7 ± 0.1 m, males: 1.77 ± 0.1 m), alcohol use (females: 2.8 ± 2.3 drinks/week, males: 5.9 ± 4.7 drinks/week) or cigarette use (no participants of either gender consumed more than 10 cigarettes/day). Body weight was found to be significantly greater in males [females: 63.9 ± 9.3 kg, males: 72.6 ± 8.0 kg, Gender main effect: $F(1,17)=4.31$, $P<.05$].

3.2. Hormone levels

Descriptive statistics for participants' salivary estradiol and salivary progesterone levels are presented in Table 1. The salivary estradiol levels were similar to those reported elsewhere for adult males and females tested across the menstrual cycle (via gum-elicited salivary method; see Shirtcliff et al., 2000). Salivary progesterone levels were approximately 130 times greater than estradiol levels across the four sessions (Table 1), a ratio that also characterizes the concentrations of these hormones in plasma (see Eriksson et al., 1994). Progesterone levels increased 2.4-fold between the follicular and luteal phases (Table 1), a pattern reported by others (Cedard et al., 1984; Zorn et al., 1984) and well within the normal range (reviewed by Bourque et al., 1986). The range of estradiol and progesterone levels presented in Table 1 indicates that the hormonal milieu of some subjects in the follicular phase may have been similar to that of other subjects in the luteal phase (since the maximum and minimum values overlap, especially for estradiol). This overlap qualifies the ability to generalize results from a sample level to any one individual. The hormone levels of female participants were subjected to a 2 (Phase) × 2 (Drug) repeated-measures ANOVA. Salivary estradiol showed an expected but nonsignificant rise between the follicular and luteal phases in females [$F(1,6) = 1.56$, n.s.]. The lack of a significant increase in estradiol levels between follicular and luteal phases implies that the salivary measurement technique may not be preferred in future studies of ovarian function. However, this is not unique to the present study. Nonsignificant differences between estradiol levels in the follicular and luteal phases of nonconception cycles have also been documented using salivary measures by other researchers (Lu et al., 1999). Salivary progesterone levels showed the expected, significant rise between the follicular and luteal phases within subjects [$F(1,5) = 10.57$, $P < .05$]. There were no differences in salivary hormones on the amphetamine or PL sessions in either menstrual cycle phase [n.s. Phase × Drug interaction: salivary estradiol, $F(1,6) = 0.20$, $P > .6$; salivary progesterone, $F(1,5) = 0.31$, $P > .6$] or across the study as a whole [n.s. Drug main effect: salivary estradiol, $F(1,6) = 3.42$, n.s.; salivary progesterone, $F(1,5) = 2.0$, n.s.]. Salivary estradiol levels assayed for male participants did not differ between the amphetamine and PL sessions [$F(1,5) = 0.72$, $P > .4$; see Table 1]. Females' estradiol levels in the luteal phase were significantly greater than the estradiol levels of males [$F(1,12) = 4.98$, $P < .05$], while this sex difference did not emerge in the follicular phase [$F(1,14) = 3.03$, n.s.].

3.3. Menstrual cycle analyses: female participants

3.3.1. AMPH effects

Effects of amphetamine in female participants are presented in the second and third columns of Table 2. Amphetamine produced its expected effects compared to PL, as amphetamine significantly increased self-reports on the ARCI-A ($P < .05$), ARCI-Benzedrine scale ($P < .01$), ARCI-Morphine–Benzedrine scale ($P < .05$), POMS-Friendliness ($P < .05$), POMS-Elation ($P < .01$), POMS-Vigor ($P < .05$), POMS-Arousal ($P < .05$), POMS-Positive Mood ($P < .01$) and SSQ Pleasant Stimulation ($P < .05$) and prevented the increase in SSQ Unpleasant Sedation that was observed under PL ($P < .05$). On physiological indices, amphetamine significantly increased systolic blood pressure ($P < .001$) and diastolic blood pressure ($P < .001$; see Table 2). In several cases, these amphetamine effects emerged mid to late in the sessions, producing significant AMPH × Time interactions (e.g., ARCI-PCAG $P < .05$; POMS-Elation $P < .01$, DEQ Feel Drug $P < .001$, DEQ Feel High $P < .05$, DEQ Want More $P < .05$, SSQ Pleasant Stimulation $P < .05$, SSQ Unpleasant Stimulation $P < .01$ and physiological outcomes Systolic BP, $P < .001$, and Heart Rate, $P < .001$; see Table 2). The AMPH × Time interaction for ARCI-PCAG sedation ($P < .05$) and SSQ Unpleasant Sedation ($P < .01$; see Table 2) reflect rises in sedation under PL versus decreases in sedation under amphetamine across the sessions.

3.3.2. Interactions between menstrual cycle phase and AMPH

Amphetamine produced differential effects in the follicular and luteal phase on several measures, as seen in the last two columns of Table 2. On the ARCI-A and ARCI-MBG

Table 1
Salivary levels of estradiol (E2) and progesterone (Prog) on PL and amphetamine sessions

	Follicular				Luteal				Men	
	PL		AMPH		PL		AMPH		PL	AMPH
	E2	Prog	E2	Prog	E2	Prog	E2	Prog	E2	E2
Mean	1.56	156.32	1.45	116.61	1.81	321.62	1.80	323.10	0.79	0.60
S.D.	1.48	89.86	0.87	59.25	0.84	135.13	1.60	153.19	0.48	0.39
Minimum	0.50	13.63	0.65	48.42	0.95	97.46	0.52	70.41	0.25	0.25
Maximum	5.39	281.41	3.48	224.69	3.54	500.02	5.48	520.18	1.57	1.31
n	10	10	11	9	8	8	8	8	6	6

Salivary levels of estradiol (E2; pg/ml) and progesterone (Prog; pg/ml) determined from baseline saliva samples obtained before the administration of PL or AMPH for female and male participants. Minimum E2 levels for male participants represent the lower limits of E2 detection in saliva.

Table 2
Significant F values (ANOVA) for main effects and interactions between the factors of Menstrual Cycle (follicular, luteal), Drug Condition (15 mg AMPH or PL) and Time (each half hour per 4.5-h session) for female participants' subjective and physiological responses to AMPH

	Phase, $F(1,11)$	AMPH, $F(1,11)$	AMPH × Time, $F(9,99)$	Phase × AMPH, $F(1,11)$	Phase × AMPH × Time, $F(9,99)$
ARCI					
Amphetamine		6.74 * A>P		5.18 * AF↑, AF>AL	1.97 * AF↑
Benzedrine		8.61 ** A>P			
MBG	7.44 * F>L	6.94 * A>P		5.17 * AF↑, AF>AL	
PCAG			2.12 * A↓P↑		2.41 *
POMS					
Friendliness		8.18 * A>P			
Elation		11.05 ** A>P	2.62 ** A↑		
Vigor		5.60 * A>P			
Arousal		6.15 * A>P			
Positive Mood		12.97 ** A>P			
DEQ					
Feel Drug			2.95 ** A↑	17.93*** AF↑, AF>AL	3.43*** AF↑>AL
Feel High			2.05 * A↑	23.18*** AF↑, AF>AL	4.79*** AF↑>AL
Want More			2.04 * A↑	10.63** AF↑	3.13** AF↑
SSQ					
Pleasant Stimulation		6.32 * A>P	2.47 * A↑		
Unpleasant Sedation		7.67 * A<P	2.51 ** A↓P↑		
Cardiovascular					
Systolic BP		21.42*** A>P	4.10*** A↑		2.10 *
Diastolic BP		29.83*** A>P	3.88*** A↑		
Heart Rate			4.76*** A↑		

Subjective responses were assessed through the empirically derived ARCI scales, the POMS scales, DEQ visual analogue items and SSQ factors. Physiological measures assessed were systolic blood pressure, diastolic blood pressure and heart rate. Direction of effects indicated for conditions: F = follicular, L = luteal, A = amphetamine, P = PL; (>) greater than condition indicated; (↑) significant rise over time under condition indicated; (↓) significant decrease over time under condition indicated.

* $P \leq .05$

** $P \leq .01$.

*** $P \leq .001$.

scales, the effects of amphetamine were greater during the follicular phase than during the luteal phase (greater at specific time points: ARCI-A Phase × AMPH × Time interaction, $P < .05$; greater overall during follicular phase: ARCI-A Phase × AMPH interaction, $P < .05$); and ARCI-MBG scale Phase × Drug interaction $P < .05$; Table 2). Means, standard deviations and pairwise comparisons for significant phase effects in drug responding are presented in Table 3.

Amphetamine also induced a larger increase in DEQ self-reports of feeling the drug effect, feeling high and wanting more drug during the follicular phase compared to the luteal phase. In contrast to ARCI-A and ARCI-MBG outcomes, the DEQ Feel Drug and Feel High ratings were significantly lower on the luteal amphetamine session compared to the luteal PL, as well as the follicular amphetamine sessions, which did not differ from each other (for pairwise comparisons, see Table 3). The DEQ Want More rating showed a less robust phase-dependent effect, as ratings on the luteal amphetamine session showed a nonsignificant trend toward being lower than the follicular amphetamine session. Ratings on all three DEQ outcomes on the luteal amphetamine phase did not differ from the follicular PL session (see Table 3). These amphetamine effects were most apparent in the mid to late portion of the amphetamine session in the follicular phase, which yielded a three-way interaction between Menstrual Phase, AMPH, and Time for these three DEQ outcomes (DEQ Feel Drug: $P < .001$; DEQ Feel High: $P < .001$; DEQ Want More: $P < .01$; see Table 2). In-depth analysis indicated that these time-dependent effects produced a rise in ratings from baseline that was significantly magnified on the follicular amphetamine compared to the luteal amphetamine sessions for Feel Drug and Feel High ratings (pairwise $P < .01$ and $P < .005$, respectively). In contrast, the Phase × AMPH × Time interaction on the ARCI-PCAG scale ($P < .05$) and systolic blood pressure ($P < .05$) appeared to reflect uninterpretable variation late in the test sessions (data not presented). Amphetamine effects did not differ between the follicular and luteal phases for any physiological measures.

The magnitude of the amphetamine-induced subjective effects during the luteal phase is informed by two specific comparisons. First, compared to amphetamine responses during the follicular phase, amphetamine responses during

Table 3
Means and standard deviations for significant interactions between amphetamine and menstrual phase conditions

	Follicular		Luteal	
	PL	AMPH	PL	AMPH
ARCI				
Amphetamine	2.48	4.01 * , * * , * * *	2.78	2.77
	(2.01)	(2.59)	(2.06)	(1.89)
MBG	2.77	5.71 * , * * , * * *	2.85	2.68
	(3.16)	(4.65)	(3.39)	(2.62)
DEQ				
Feel Drug	1.05	2.16 * , * * *	1.71 * * *	0.95
	(1.85)	(2.51)	(1.99)	(1.58)
Feel High	0.75	1.66 * , * * *	1.30 * , * * *	0.56
	(1.57)	(2.21)	(1.71)	(0.99)
Want More	1.70	2.62 *	2.68 *	1.90
	(2.23)	(2.73)	(2.67)	(2.26)

Least-squared means and standard deviations (in parentheses) for outcomes with significant Drug × Phase interactions (F values are presented in Table 2). Data are for PL and Amphetamine (AMPH) sessions during the follicular and luteal phases for female participants. Significant outcomes included self-reports of subjective effects on the ARCI-A scale, ARCI-MBG scale and DEQ items "Feel Drug", "Feel High" and "Want More". Fisher LSD comparisons.

* Different from follicular PL, $P<.05$.

* * Different from luteal PL, $P<.05$.

* * * Different from luteal amphetamine, $P<.05$.

the luteal phase were significantly lower on four of five outcomes (ARCI-A, ARCI-MBG, DEQ Feel Drug, DEQ Feel High; see *** in Table 3). Second, within the luteal phase, female participants could not distinguish between PL and amphetamine for three outcomes (ARCI-A, ARCI-MBG and DEQ Want More effects), and showed blunted amphetamine responses compared to PL for two outcomes (DEQ Feel Drug, DEQ Feel High; see *** in Table 3). These data indicate that females' responses to amphetamine in the luteal phase are blunted compared to the follicular phase and that females' responses to amphetamine in the luteal phase are also either blunted or equal to their responses to PL in the luteal phase (Fig. 1a,b). Thus, the mood effects of amphetamine in the luteal phase do not rise to the level of positive effects achieved after PL for several outcomes.

3.3.3. Mediation of menstrual phase effects by salivary hormones

To determine whether the observed menstrual cycle differences in amphetamine's effects are mediated by salivary levels of estradiol and progesterone, salivary estradiol and progesterone levels were entered as changing covariates in a series of 2 (Phase) × 2 (AMPH) repeated-measures ANCOVAs. In each case, covariation for salivary estradiol and progesterone levels caused the observed Phase × AMPH interactions to become nonsignificant [ARCI-A, $F(1,3)=0.99$, $P=.4$; ARCI-MBG, $F(1,3)=0.86$, $P=.4$; ARCI-PCAG, $F(1,3)=0.003$, $P=.96$; DEQ Feel Drug, $F(1,3)=0.33$, $P=.61$; DEQ Feel High, $F(1,3)=6.1$, $P=.09$; DEQ Want More, $F(1,3)=0.1$, $P=.77$; Systolic BP, $F(1,3)=6.1$, $P=.09$]. The observed Phase × AMPH interactions also became nonsignificant when estradiol and progesterone covariates were assessed separately, an effect that was more marked for progesterone than estradiol for three of the seven outcomes [Progesterone ANCOVA Phase × AMPH effects: DEQ Feel Drug, $F(1,4)=0.20$, $P=.68$; DEQ Feel High, $F(1,4)=2.33$, $P=.20$; Systolic BP, $F(1,4)=0.5$, $P=.51$; vs. Estradiol ANCOVA Phase × AMPH effects: DEQ Feel Drug, $F(1,5)=1.37$, $P=.29$; DEQ Feel High, $F(1,5)=5.28$, $P=.07$; Systolic BP, $F(1,5)=1.4$, $P=.29$]. These data indicate that the observed menstrual cycle differences in amphetamine's effects are mediated by both the salivary levels of estradiol and progesterone, with some evidence that progesterone may more important for several of these effects.

3.4. Gender differences analyses

3.4.1. Gender differences

Males scored higher on POMS Arousal than females tested in either the follicular [$F(1,17)=5.05$, $P<.05$] or luteal [$F(1,17)=4.95$, $P<.05$] phases, irrespective of drug condition.

3.4.2. Gender differences in AMPH responding

Responses to amphetamine did not differ between males and females tested in the follicular phase on any measure from the ARCI, DEQ or POMS.

In contrast, a number of gender differences emerged when males' AMPH responses were compared with females' AMPH responses in the luteal phase. Males were more responsive to amphetamine than females in the luteal phase on ARCI-A [$F(1,17)=5.45$, $P<.05$], ARCI-MBG [$F(1,17)=5.60$, $P<.05$], DEQ Feel Drug [$F(1,17)=16.07$, $P<.001$] and DEQ Want More [$F(1,17)=10.69$, $P<.005$]. Gender differences in amphetamine-induced ARCI-A responses are presented in Fig. 1a and b as representative of these effects.

3.5. Influence of endogenous steroids

3.5.1. Relationship between hormones and response to AMPH

The levels of estradiol and progesterone obtained before administration of capsules on the PL and amphetamine sessions appear in Table 1. These levels are within the range expected for these phases of the cycle (Shirtcliff et al., 2000; Ellison, 1993). In the follicular phase, progesterone and estradiol levels were uncorrelated with menstrual cycle day (all r's $<|.4|$, $P=$ n.s.), and were positively associated ($r=.53$, $P=$ n.s. on AMPH session; $r=.63$, $P<.05$ on PL session). The lack of a correlation between these levels and menstrual cycle day was unexpected and suggests that the salivary measures may have underestimated serum levels of these hormones in the current sample (see Shirtcliff et al., 2000).

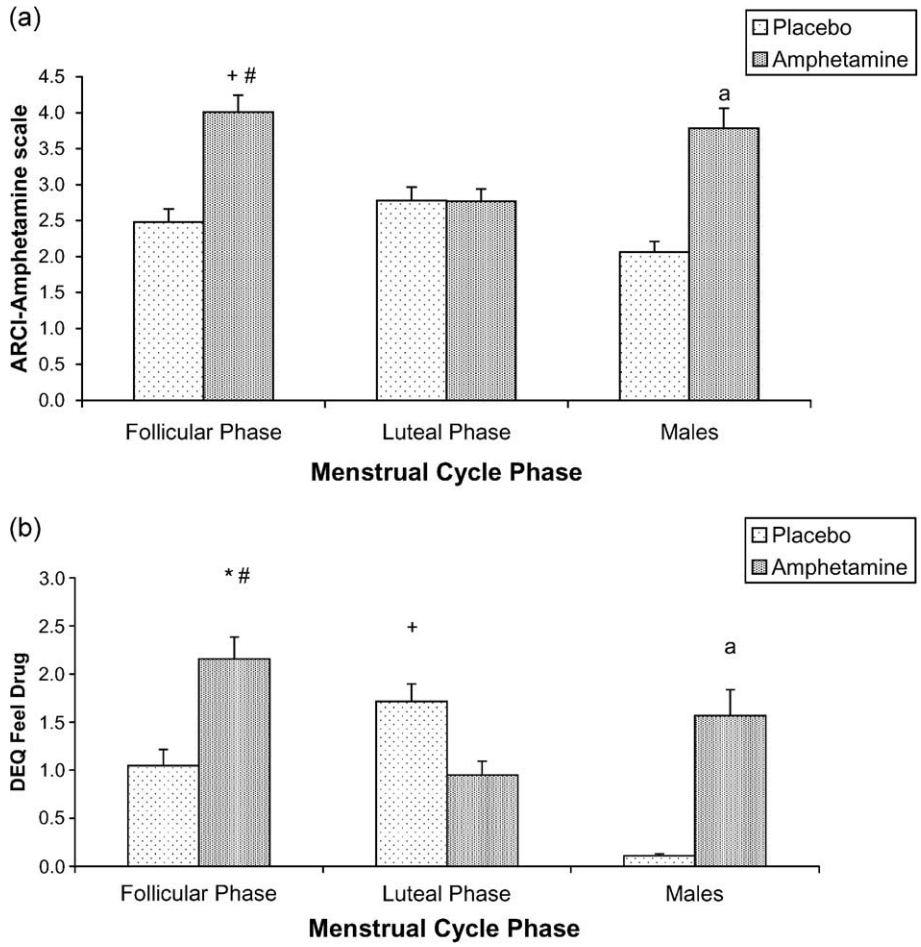

Fig. 1. (a) Effects of amphetamine and PL on mean ARCI-A (amphetamine scale) scores by menstrual phase and gender. The self-reported subjective stimulant effects of amphetamine differed between the follicular and luteal phases of the same menstrual cycle for female participants (left portion of the figure); Phase × Drug interaction, ARCI-A scale: $F(1,10) = 5.18$, $P < .05$, as the ARCI-A scores during the luteal phase were almost identical between the PL and amphetamine sessions. Male participants' self-reports on the ARCI-A scale are presented on the right portion of the figure. Subjective effects of amphetamine differed only between men and women tested in the luteal phase. + = Differs from follicular PL condition, $P < .01$; # = differs from luteal PL and luteal amphetamine, $P < .05$; a = Gender × Drug interaction [$F(1,17) = 5.45$, $P < .05$] with luteal phase responses. (b) Effects of amphetamine and PL on mean DEQ Feel Drug scores by menstrual phase and gender. The self-reported subjective effects of amphetamine differed between the follicular and luteal phases of the same menstrual cycle for female participants (left portion of the figure); Phase × Drug interaction, DEQ Feel Drug: $F(1,11) = 17.93$, $P < .001$. The DEQ Feel Drug scores during the luteal phase were less than PL responses during the luteal phase. Male participants' self-reports on the DEQ Feel Drug scale are presented on the right portion of the figure. Subjective effects of amphetamine differed only between men and women tested in the luteal phase. * = Differs from follicular PL condition, $P < .05$; # = differs from luteal PL and luteal amphetamine, $P < .05$; + = differs from luteal amphetamine, $P < .05$; a = Gender × Drug interaction [$F(1,17) = 16.07$, $P < .001$] with luteal phase responses.

To test the potential contributions of endogenous hormones to amphetamine responsivity, correlations were performed between baseline (pre-AMPH) salivary estradiol and progesterone levels and the AMPH-induced peak changes (peak minus predrug baseline score) on dependent measures on the follicular and luteal AMPH sessions in females. Significant correlations for the follicular phase are presented in Table 4. Positive correlations obtained between baseline salivary estradiol levels on the follicular amphetamine session and the magnitude of the amphetamine-induced rise in POMS Elation ($r = .78$, $P < .01$), POMS Vigor ($r = .55$, $P < .05$), POMS Positive Mood ($r = .72$, $P < .01$) and Heart Rate ($r = .60$, $P < .05$). These data indicate that the positive mood effects of amphetamine increase with increasing estradiol. A scatterplot of the relationship with amphetamine-induced POMS Elation is presented in Fig. 2a as representative of these effects. The high-estradiol datapoint seen in Fig. 2a was characteristic. Exclusion of this high-influence point caused each of the correlations presented in Table 4 with estradiol to become nonsignificant ($P > .2$) or marginally significant (Heart Rate, $r = .41$, $P = .11$).

In contrast, baseline salivary progesterone levels in the follicular phase were moderately to strongly negatively related to the positive mood effects of amphetamine (Table 4). Progesterone significantly depressed POMS Friendliness ($r = -.66$, $P < .05$) and SSQ Pleasant Sedation ($r = -.68$, $P < .05$) and marginally depressed amphetamine-induced changes on the ARCI-A ($r = -.54$, $P < .10$; data not shown).

Table 4
Significant correlations between baseline levels of ovarian hormones and responses to amphetamine in the follicular phase

	Salivary estradiol	Salivary progesterone	E2/P
POMS			
Friendliness		− 0.66 *	
Elation	0.78**		
Vigor	0.55 *		
Positive Mood	0.72**		
DEQ			
Like Drug			0.64 *
SSQ			
Pleasant Sedation		− 0.68 *	
Heart Rate	0.60 *		
n	11	10	9

The magnitude of individuals' subjective and physiological responses to amphetamine was assessed through the peak change (postcapsule minus baseline precapsule values) observed on dependent measures assessed on the follicular amphetamine testing session in female participants. Significant correlations obtained between salivary levels of estradiol (E2), progesterone (P) and the ratio between estradiol and progesterone (E2/P) on the follicular amphetamine session with the magnitude of precapsule to postcapsule change in self-reported subjective effects on the POMS Friendliness, Elation, Vigor and Positive Mood scales; the DEQ "Like Drug" item; the SSQ Pleasant Sedation factor; and on objective physiological measures of heart rate.

* $P < .05$.

** $P < .01$, one-tailed.

The scatterplot of the amphetamine-induced POMS Friendliness data is presented in Fig. 2b as representative of these progesterone effects. As seen in Fig. 2b, the association between progesterone and amphetamine subjective effects did not involve high-influence outliers. Moreover, the source of these individual differences in progesterone levels in the follicular phase did not appear to be menstrual cycle day, as the relationship between cycle day and progesterone levels during the follicular session was nonsignificant ($r = .25$, $P > .26$, $n = 9$). The size and direction of the progesterone effects described in Table 4 remained significant after controlling for estradiol (e.g., SSQ Pleasant sedation: partial $r = -.69$, $P < .05$ with salivary progesterone). These data collectively indicate that higher levels of progesterone were associated with less positive mood effects of amphetamine. This finding is likely a conservative estimate of the effects of progesterone on amphetamine responding, as progesterone levels are relatively low in the follicular phase (see Table 1). In addition, these findings are consistent with the dampened positive subjective effects of amphetamine in the luteal phase compared to the follicular phase in these participants, and with the gender difference that emerges in the luteal phase when progesterone levels are elevated (e.g., Fig. 1a,b).

The joint effects of estradiol and progesterone on amphetamine responding can be addressed through the ratio between salivary estradiol and progesterone (higher ratios indicating greater levels of estradiol compared to progesterone), which was associated with heightened heightened drug liking (DEQ Like Drug, $r = .64$, $P < .05$; Table 4) and

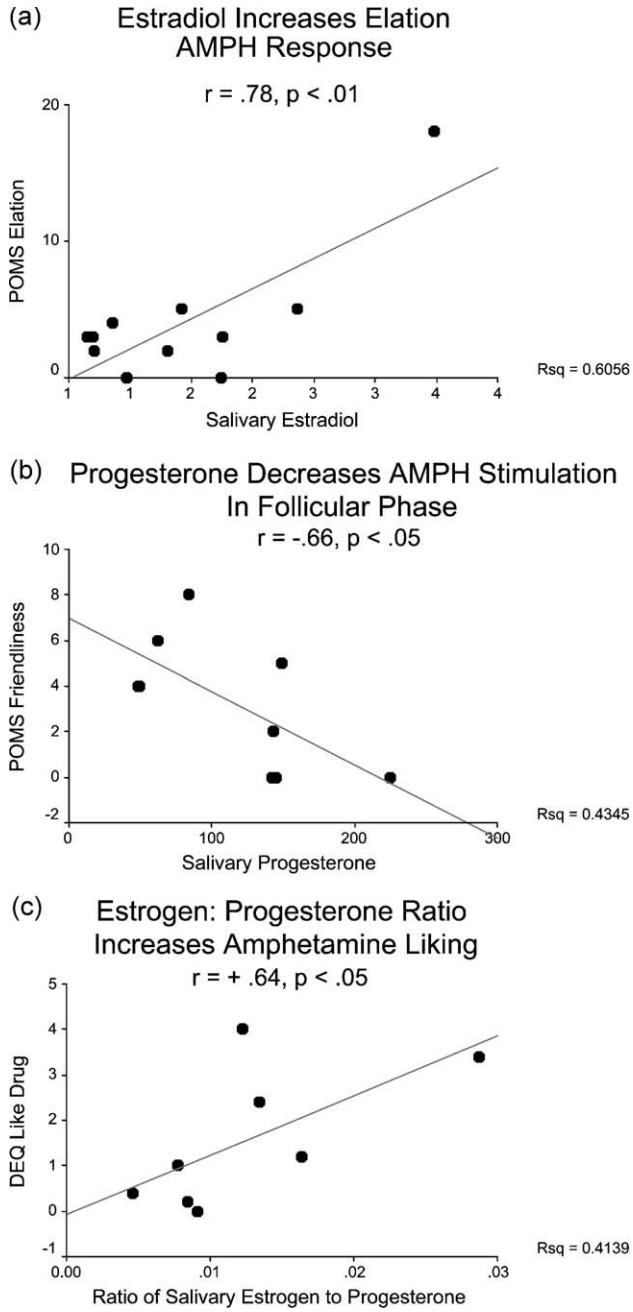

Fig. 2. (a) Precapsule salivary estradiol (pg/ml) is positively associated with the amphetamine-induced increase in self-report ratings on the POMS Elation scale (postcapsule peak minus precapsule baseline) on the follicular amphetamine session for female participants ($n = 11$). Relationship becomes not significant after exclusion of rightmost datapoint. (b) Precapsule salivary progesterone (pg/ml) is negatively associated with the amphetamine-induced increase in self-report ratings on the POMS Friendliness scale (postcapsule peak minus precapsule baseline) on the follicular amphetamine session for female participants ($n = 10$). (c) The ratio between precapsule salivary estradiol (pg/ml) and precapsule salivary progesterone (pg/ml) is positively associated with the amphetamine-induced increase in self-report ratings on the DEQ "Like Drug" visual analogue item (postcapsule peak minus precapsule baseline) on the follicular amphetamine session for female participants ($n = 9$).

marginally elevated POMS Elation (r=.56, P<.10; data not shown) after amphetamine in the follicular phase. The scatterplot of amphetamine-induced drug liking with the follicular estradiol/progesterone ratio is presented in Fig. 2c. This correlation did not include the high-estradiol datapoint discussed above. This correlation also maintained in size and direction after elimination of the most extreme (rightmost) datapoint in Fig. 2c (DEQ Like Drug, r=.51), despite a decrease in statistical power (P=.11).

To test whether these associations between endogenous hormones and amphetamine responses also hold in the luteal phase, correlations were performed between baseline (pre-AMPH) salivary estradiol and progesterone levels and the AMPH-induced peak changes (peak minus predrug baseline score) on dependent measures on the luteal AMPH session for females. The truncated range of amphetamine responses and the elevated hormone levels in the luteal phase would be expected to minimize the predictable variation, and therefore the ability to see significant relationships during this phase. Most of the relationships presented in Table 4 for the follicular phase were nonsignificant in the luteal phase, with one exception. There was a strong positive relationship between amphetamine-induced heart rate and salivary progesterone levels (r=.76, P<.05, n=8) in the luteal phase. While this suggests that the hormone determinants of heart rate responses to amphetamine differ in the follicular and luteal phases, this result could reflect the moderate correlation between estradiol and progesterone in the follicular amphetamine session (r=.48, P=.11, n=8). However, after controlling for the contributions of estradiol to amphetamine-induced heart rate, the association between luteal progesterone and luteal amphetamine-induced heart rate change remains significant (partial r=.69, P<.05, n=5). While this finding will require replication using more reliable plasma measures of these hormones (see Shirtcliff et al., 2000), this finding suggests that the cardiovascular and subjective effects of amphetamine may be differentially related to ovarian hormones across the menstrual cycle.

4. Discussion

There were four major findings of the present study. First, women reported heightened mood responses to AMPH during the follicular phase compared to the luteal phase. Second, men reported responses to AMPH that differed from those of women tested during the luteal, but not the follicular, phase (see Fig. 1a,b). Third, the modest positive correlations between estradiol levels and the stimulant effects of AMPH reflected the effects of one high-influence datapoint. Fourth, there were robust inverse relations between progesterone levels and the stimulant effects of AMPH in women during the follicular phase. These four findings and their implications are discussed below.

The observation that subjective responses to amphetamine were greater during follicular than the luteal phase in women is consistent with previous findings, which indicated that amphetamine-induced euphoria (ARCI-MBG), energy and intellectual efficiency (ARCI-BG) and "drug high" (DEQ) are heightened in the follicular compared to the luteal phase in normally cycling women (Justice and de Wit, 1999). The current findings that amphetamine-induced stimulation (ARCI-A), euphoria and motivation (ARCI-MBG), magnitude of feeling the drug effect, feeling "high" and wanting more drug (DEQ measures) are heightened in the follicular phase strongly replicates the original menstrual phase effects in an independent sample and extends these results to several additional mood measures not previously identified.

The second finding concerns sex differences in responses to amphetamine, which in the current study were directly related to variations across the menstrual cycle in females' amphetamine responding. Males' responses to amphetamine were not significantly different from those of women tested during the follicular phase, when levels of progesterone are low and when stimulant amphetamine effects were maximal for female participants. In contrast, males' responses were significantly different from those of women tested during the luteal phase, when levels of progesterone are high and when stimulant amphetamine effects were blunted for female participants. This pattern is consistent with that observed by Sofuoglu et al. (1999) in males' and females' responses to cocaine. These findings support the idea that gender differences in AMPH responding do not reflect broad-based neural differences in responses to AMPH between men and women, but rather, a temporally plastic modulation of the neural systems involved in stimulant drug responding by circulating steroid hormones.

While the mechanism behind the observed phase difference in AMPH effects cannot be definitively answered by the current study, the ANCOVA results and two results concerning between-subjects variation in maximal AMPH responses suggest that circulating endogenous hormones play a role in the above phase effects. First, the salivary levels of estradiol and progesterone appeared to mediate the observed menstrual phase differences in amphetamine's effects when entered as repeated measures covariates, with some evidence that progesterone levels were somewhat more effective mediators of these effects. Second, in the correlational analyses, higher levels of progesterone were associated with dampened stimulant effects of amphetamine during the follicular phase (Table 4; Fig. 2b). These effects of endogenous progesterone are consistent with a recent report that exogenous progesterone administered during the follicular phase significantly dampened craving for cigarettes and reduced the self-reported "good effects" of smoking (Sofuoglu et al., 2001). The relationship between progesterone and response to amphetamine in the current study emerged even though progesterone levels during the follicular phase are very low, which should have worked against the latter finding. Overall, these data suggest that elevated progesterone in the luteal phase

mediates the observed menstrual phase differences in amphetamine effects.

These data also suggest that individual differences in endogenous progesterone may be an important determinant of between-subjects variation in amphetamine responsivity in normal women. Such variation can stem from between-subjects differences in age, ethnicity, dieting history and physical activity (for a review, see Ellison, 1993), though other factors may also play a role. The contribution of biologically available progesterone to ongoing emotional states is supported by the recent findings that exogenous progesterone can produce moderate decreases in positive mood states (i.e., decreases in Vigor and Friendliness scales of the POMS) in normally cycling women (de Wit et al., 2001). However, the relationship between progesterone and mood is not fully understood. Some researchers suggest that time-dependent fluctuations, rather than absolute levels, of progesterone are better predictors of negative emotional outcomes (Halbreich et al., 1986), and a number of studies have failed to find any relationship between progesterone levels and normal mood (Abplanalp et al., 1979; Laessle et al., 1990). In contrast, the current progesterone results suggest that absolute levels of progesterone may be an important modulator of emotional systems, dampening the subjective effects of incoming emotionally relevant stimuli in both the luteal and follicular phases.

The final finding of the current study was a positive association between salivary estradiol level and amphetamine-induced Elation, Vigor, Positive Mood (POMS) and heart rate in women during the follicular phase. These relationships appear fragile, however, given that a high-influence datapoint significantly contributed to these effects (see Fig. 2a). Whether the existence of high-influence points should negate these findings is, however, unclear. The exclusion of this high-influence datapoint fails to entirely eliminate the relationship between drug liking and the estradiol/progesterone ratio in the follicular phase (see Fig. 2c), and the current associations with estradiol are strikingly similar to previous results concerning plasma estradiol and mood responses to AMPH (e.g., Justice and de Wit, 1999). Positive mood (POMS Vigor) is also elevated on days of the menstrual cycle where plasma estradiol reaches a peak, though these mood effects are small and not entirely stable over consecutive cycles (Abplanalp et al., 1979). Moreover, recently published concerns about the potential underestimation of estradiol–behavior relationships by salivary estradiol (see Shirtcliff et al., 2000) may have worked against the ability to see a more robust association between estradiol and amphetamine responsivity in the current study. Thus, the present estradiol findings do not constitute unequivocal support for the possibility that estradiol facilitates stimulant responding. A discrete mechanism does, however, exist to explain the increased euphoric effects of amphetamine under conditions of high estradiol. Bioavailable estradiol (which, in saliva, closely reflects the unbound fraction of serum estradiol; see Vining et al., 1983) immediately activates dopamine synthesis through phosphorylation of its rate-limiting enzyme TH (Pasqualini et al., 1995, 1996) and effectively increases cytosolic dopamine available for subsequent release by amphetamine. As outliers have previously characterized estradiol effects in studies using nonsalivary analysis techniques (e.g., Justice and de Wit, 1999), these data suggest that future study of these amphetamine effects may be warranted. Nonetheless, the current data do not provide unequivocal evidence of an association between estradiol and stimulant responding.

The above four major findings concerning menstrual phase, gender, estradiol and progesterone associations with amphetamine responses have several implications for basic and clinical research. First, women who initially use a stimulant drug for recreational purposes during the follicular phase may be more likely to repeat use of the drug because of its stronger effects. Second, female addicts who are trying to abstain from drug use may be more likely to succeed if the initial abstinence is scheduled to occur during the luteal phase, when the drug effects are less potent. Third, the dampened responses to stimulants during the luteal phase may protect women from the risk of use escalation or abuse, because they are expected to be in the luteal phase roughly 46% of the time. In contrast, males may be more at risk for stimulant use than females because they experience the drug maximally on more occasions. Fifth, these findings have direct implications for the investigation of individual differences in responses to amphetamine and suggest that women should be tested during the follicular phase when drug effects are maximal.

Future investigation of the precise neural mechanisms mediating these steroid and menstrual phase effects seems warranted. It will be important to examine the involvement of dopamine in the fluctuation in the stimulant effects of amphetamine across the menstrual cycle. Neuroimaging data indicate that the intensity of the subjective "high" induced by dopamine agonists (e.g., AMPH, methylphenidate) is significantly correlated with the levels of drug-induced dopamine release in human PET experiments ($r>|.9|$, Drevets et al., 2001; $r=.78$, Volkow et al., 1999). This suggests that the heightened stimulant effects of amphetamine in the follicular phase (e.g., "feel high"; Table 2) in the current study may reflect a time-dependent up-regulation of mesolimbic and mesocortical dopamine systems during the follicular phase. To date, however, markers of basal dopamine function do not appear to vary as a function of cycle phase. For instance, plasma and CSF levels of the dopamine metabolite HVA (Abel et al., 1996; Eriksson et al., 1994), as well as PET-determined D2 receptor density (Nordstrom et al., 1998), have not been found to vary between the follicular and luteal phases in normal women and are uncorrelated with either estradiol or progesterone across the cycle (Abel et al., 1996). As such, the mechanism behind the present menstrual phase and steroid-associated variation in amphetamine effects requires additional investigation.

To sum up, the results of the current study are fourfold. First, the current study replicated and extended previous findings such that effects of AMPH appear to be fairly strongly and reliably influenced by menstrual cycle phase. Second, gender differences in AMPH responding emerge almost entirely as a function of menstrual cycle phase variation in female responses to amphetamine. Third, in normally cycling adult women, the internal hormonal milieu is fairly strongly associated with the magnitude of the maximal psychological effects of AMPH. Progesterone is associated with dampened stimulant responding in the follicular phase, when progesterone levels are relatively minimal and amphetamine responses are relatively maximal. Fourth, the current study provided only limited evidence that estradiol might facilitate stimulant responding. Future studies will be required to investigate the extent to which dopamine and other neurotransmitter systems are involved in the modulation of agonist drug effects by endogenous steroids.

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