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Progesterone treatment during the early follicular phase of the menstrual cycle: Effects on smoking behavior in women

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Abstract

The goals of this study were (1) to examine the feasibility of administering progesterone to women during the early follicular phase when the endogenous estradiol and progesterone levels are low, and (2) to investigate the effects of oral progesterone treatment on smoking behavior in female smokers. Twelve subjects had two experimental sessions, within 3–9 days after the beginning of their menses. In each experimental session, subjects received a single 200-mg dose of progesterone or placebo, orally. Two and a half hours after the medication treatment, subjects were assessed for subjective response to two puffs of a cigarette and then started the self-administration period in which they had the option to exchange their token for two puffs of cigarette, 15 min apart. Subjects had low levels of estradiol and progesterone before the first and second sessions. Plasma progesterone levels peaked in 2 h following progesterone treatment. Progesterone treatment attenuated the craving for and subjective effects from smoking. Under progesterone treatment, there was a trend for decreased smoking behavior. These preliminary results suggest that the early follicular phase of the menstrual cycle may be a useful interval to investigate the effects of exogenous progesterone in female smokers. The effects of progesterone on nicotine dependence need to be studied further.

Keywords: Progesterone; Micronized progesterone; Smoking behavior; Women; Menstrual cycle; Early follicular phase

1. Introduction

Evidence suggest that response to drugs of abuse in humans may be affected by the phase of the menstrual cycle in women. In a recent study with crack cocaine users, women in the luteal phase reported diminished ratings of subjective effects of cocaine, compared with women in the follicular phase of their menstrual cycle (Sofuoglu et al., 1999). Similarly, in normal volunteers, diminished response to amphetamines were observed during the luteal phase, compared with the follicular phase of the menstrual cycle (Justice and de Wit, 1999). For nicotine, a recent study found no menstrual cycle effects on the subjective and physiological response to nicotine nasal spray (Marks et al., 1999). In contrast, in another study, women in the luteal phase of their menstrual cycle reported diminished analgesic effects from nicotine patch compared with men (Jamner et al., 1998). These results support the importance of the menstrual cycle phase in response to stimulant drugs in women. An important question is whether the phase of the menstrual cycle also modulates drug use behavior. There is evidence to suggest that alcohol intake may increase during the late luteal phase of the menstrual cycle (Harvey and Beckman, 1985; Mello et al., 1990). Menstrual cycle phase may also affect smoking behavior in women. Around menses and during the late luteal phase, increased smoking behavior was reported in some (DeBon et al., 1995; Mello et al., 1987; Snively et al., 2000) but not all the studies (Allen et al., 1996; Pomerleau et al., 1994). The effects of menstrual cycle phase on drug use behavior for other stimulants like cocaine and amphetamines have not been well studied.

These observed menstrual cycle effects on drug responses are likely mediated by the sex hormones, estradiol and progesterone. Both progesterone and estradiol interact with multiple neurotransmitter systems in the brain

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(Joels, 1997; McEwen, 1996; McEwen et al., 1997). Estradiol has been linked to lowered seizure threshold, increased locomotor activity, improved attention, and euphoria. Progesterone, on the other hand, has been associated with antianxiety, increased seizure threshold, mood stabilizing and in higher doses, anesthetic effects (Smith, 1994). However, it has been difficult to understand the exact role of each hormone on the observed menstrual cycle effects in drug response. The changing levels of estradiol and progesterone within each phase of the menstrual cycle makes it difficult to attribute a menstrual phase effect to a single sex hormone. In addition, a complex interaction exists between estradiol and progesterone, which may be synergistic or antagonistic depending on their concentrations (Graham and Clarke, 1997). Thus, interpretation of estradiol or progesterone effects may require consideration of both hormone levels. Considering the complexity of the menstrual cycle, a better understanding of the role of the sex hormones in the observed menstrual cycle effects may require new approaches.

The main goal of this study was to determine whether the early follicular phase of the menstrual cycle can be utilized to investigate the effects of exogenous sex hormones in normally menstruating women. In some previous studies on progesterone effects in women, subjects were postmenopausal (McAuley et al., 1995; Schweizer et al., 1995) or on oral contraceptives (Freeman et al., 1993), to minimize the effects from changing levels of endogenous sex hormones. While these approaches have their strengths, the generalizabilty of their results to normally menstruating women may be limited. The advantage of the early follicular phase is the low endogenous estradiol and progesterone concentrations (Yen et al., 1999), which may minimize the interaction between these hormones. We focused on the effect of micronized progesterone treatment, given during the early follicular phase, on smoking behavior in women. We chose progesterone treatment since previous studies suggest that progesterone may inhibit the effects of stimulant drugs (Justice and de Wit, 1999; Sofuoglu et al., 1999). The effects of progesterone on smoking behavior in women were investigated using a laboratory self-administration model.

2. Method

2.1. Subjects

Twelve female smokers with an average age (S.D.) of 29.0 (6.0) were recruited from the Minneapolis/St. Paul area by newspaper advertisements. On average, subjects smoked 20 (3.5) cigarettes/day, had a duration of 11.4 (6.6) years of smoking and had made an average of 2.5 (1.7) quitting attempts. Subjects were in good health as verified by medical history, screening examination, and laboratory tests. Subjects were excluded if they had irregular menses, were pregnant, breast feeding, using hormonal contraceptives, or had a history of psychotropic medication use within the last 6 months.

2.2. Procedure

This outpatient, double-blind, placebo-controlled, crossover study had one adaptation and two experimental sessions. Subjects had an adaptation session within 1 week prior to the first day of their menses. In the adaptation session, subjects were oriented to the laboratory procedures and computer task and inhaled two puffs of cigarette for 3 s, 20 s apart to become familiar with the self-administration procedure. Two experimental sessions were held from Days 3 to 9, Day 1 being the first day of menstrual cycle, starting around 9:00 a.m. The sessions were at least 2 days apart, in order to minimize the carryover effect from the study medication. Subjects were instructed to abstain from smoking after midnight on the experimental days. Abstinence from smoking was verified by breath carbon monoxide levels less than 10 ppm. In each of the experimental sessions, subjects had medication treatment followed by nicotine self-administration period. The study medication was administered after baseline measures were obtained and an hour later was followed by a light meal. The self-administration period started 2.5 h after medication administration, when peak levels of progesterone were expected, and lasted 2.5 h.

The self-administration model was adapted from our cocaine self-administration model (Hatsukami et al., 1994) and a nicotine self-administration developed by Perkins et al. (1994). It consists of two periods: work and self-administration. During the work period, subjects had the option to earn a total of 10 tokens by working on a task. The task was a computerized arithmetic task and subjects had to solve 100 problems in order to receive one token. The tokens could later be exchanged for their money value or for two puffs of cigarette during the self-administration period. The token value was US$2 for the first six subjects and US$1 for the rest of the subjects. The token value was decreased to US$1 in order to increase the low token exchange rate that was observed under US$2 condition. The self-administration period started with a sampling dose of nicotine. This was two puffs of a cigarette with a duration of 3 s each and 20 s apart. Starting 15 min afterwards and every 15 min for 2-1/2 h, subjects had the option to exchange their tokens for deliveries of two puffs of a cigarette.

2.3. Progesterone administration

During each session, subjects were given 200 mg micronized progesterone (Prometrium, Solvay Pharmaceuticals, Marietta, Georgia) or placebo. After oral administration, micronized progesterone reaches its peak plasma levels

in 2 to 3 h and has an elimination half-life of 3 to 4 h (de Lignieres, 1999; McAuley et al., 1996).

2.4. Outcome measures

The outcome measures were biochemical, physiological, behavioral, and subjective measures. The biochemical measures included plasma levels of estradiol, progesterone, nicotine, and cotinine. Plasma estradiol and progesterone levels were measured before each session to verify that subjects were in early follicular phase of their menstrual cycle. Plasma progesterone levels were also measured 1, 2, 3, and 4 h after progesterone or placebo administration. Plasma nicotine and cotinine levels were measured before each session to verify abstinence and level of smoking, respectively. The physiological measures were heart rate and blood pressure that were taken before medication treatment and every 15 min until the end of the sessions. The behavioral measure was the number of puffs smoked during the self-administration. The subjective measures included Nicotine Withdrawal Symptom Checklist (NWSC), Drug Effects Questionnaire (DEQ), and Profile of Mood States (POMS). NWSC was given before and after each session and 1 min before and 3 min after the sample smoking, which was provided 15 min before the beginning of smoking self-administration. NWSC measures withdrawal symptoms from nicotine and includes items of cigarette craving, irritability/anger, anxiety/tension, difficulty concentrating, restlessness, increased appetite, depressed mood, and insomnia (Hughes and Hatsukami, 1986, 1997). Subjects were asked to rate these symptoms from 0 (*not present*) to 4 (*severe*). In addition, subjects were asked what percentage of time they had urges for smoking. DEQ was used to measure acute effects from smoking and consisted of four items: feel the drug strength, good effects, bad effects, and head rush. Subjects rated these effects on a 100-mm scale, from "not at all" to "extremely." DEQ was given 3 min after the sampling dose. POMS, a 72-item rating scale (McNair et al., 1971), was used to measure the effects of progesterone on the subjective aspects of mood. POMS has six subscales: (1) composed–anxious; (2) agreeable–hostile; (3) elated–depressed; (4) confident–unsure; (5) energetic–tired; (6) clear headed–confused. POMS was given before and at the end of each experimental session.

2.5. Statistical analysis

The physiological and subjective measures were analyzed using repeated measures analysis. In these analyses, the main effect for the two within-subject factors, treatment and time and their interaction were included. Huynh–Feldt adjustments were used to correct for possible violations of sphericity assumption. The token exchange data were analyzed using paired t test. For all these analyses, a significance level of .05 was used.

3. Results

3.1. Biochemical measurements

Changes in progesterone levels in response to progesterone and placebo treatment, together are shown in Fig. 1. There were no significant differences in baseline progesterone levels under two treatment conditions ($P > .05$). As expected, progesterone administration increased plasma progesterone significantly compared to placebo [$F(1,11) = 25.9$, $P < .0001$].

Baseline estradiol levels were similar for placebo and progesterone treatment days, 67 (27.7) and 53.5 (22.6) pg/ml, respectively ($P > .05$). To address whether the interval between the two sessions was associated with changing baseline sex hormone levels, plasma estradiol and progesterone levels, measured before each session, were compared. The average plasma estradiol were: 50.1 (20.3) and 64.9 (27.4) pg/ml for the first and second sessions ($P > .05$). The corresponding figures were 1.4 (0.6) and 1.5 (0.7) ng/ml for the progesterone levels ($P > .05$).

Baseline cotinine levels were 225.6 (81.9) and 251.0 (113.8) ng/ml for the placebo and progesterone treatment days. The corresponding figures for plasma nicotine were 8.6 (5.7) and 10.5 (5.6) ng/ml, respectively. There were no treatment differences in baseline nicotine and cotinine levels ($P > .05$).

3.2. Physiological measurements

For heart rate, systolic and diastolic blood pressure, there were no differences in baseline measures or response to placebo or progesterone treatment ($P > .05$).

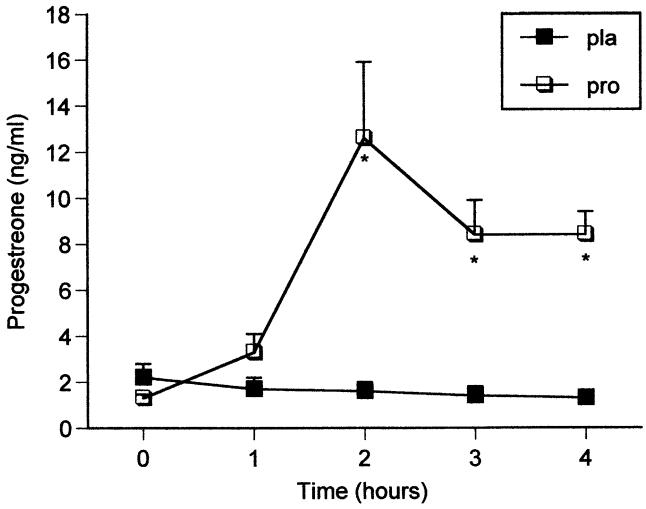

Fig. 1. The average (S.E.M.) plasma progesterone following 200 mg progesterone or placebo treatment of 12 female smokers. * indicates significant treatment differences.

3.3. Subjective measurements

The DEQ ratings of the sample smoking under two treatment conditions are shown in Fig. 2. Overall, the subjective response to sample smoking diminished with progesterone treatment, compared to placebo treatment, reaching statistical significance for ratings of good effects [$t(11)=2.4$, $P=.02$].

There were no treatment effects on the total score of eight-item NWSC. For individual items of NWSC, progesterone treatment was associated with a decreased craving for cigarettes [$F(1,11)=6.0$, $P=.032$] (Fig. 3). There was no time or Treatment × Time interaction effect. Pairwise comparisons revealed significant treatment effects for the measure taken before the sample dose ($P=.05$), 2.5 h following progesterone or placebo treatment. Similarly, for "what percentage of time you have strong urges to smoke cigarettes" there was a significant treatment effect [$F(1,11)=8.6$. $P=.014$], with lower ratings under progesterone treatment. Pairwise comparisons revealed significant treatment effects at the beginning of the session ($P=.03$) and after the sample dose ($P=.008$).

There was a significant Treatment × Time effect on the energetic–tired subscale of POMS, increased tiredness under progesterone treatment [$F(1,11)=6.9$, $P=.023$].

3.4. Behavioral measurements

Subjects earned all the available tokens, 10 tokens per session for each subject and for all subjects a total of 120 tokens under each treatment condition. Subjects exchanged a total of 46 and 28 tokens, for puffs of cigarette under placebo and progesterone treatment conditions, respectively. The average (S.D.) number of tokens exchanged for puffs of cigarettes were 3.8 (3.4) for placebo and 2.3 (2.0) for the progesterone group. The decrease in smoking behavior under progesterone treatment did not reach statistical significance [$t(11)=1.7$, $P=.1$]. The smoking self-administration was similar for US$2 and US$1 token value conditions ($P>.05$).

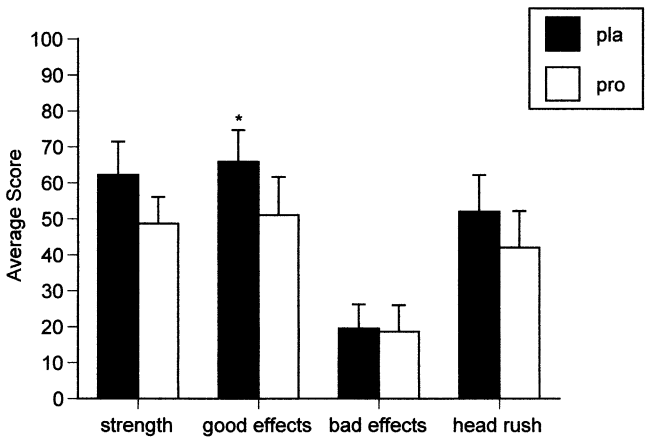

Fig. 2. Treatment effects on the subjective response to sample smoking, following overnight abstinence from smoking. Bars represent the average (S.E.M.) responses of 12 female smokers. * indicates significant treatment differences. The measurements were obtained 2.5 h following an oral dose of 200 progesterone or placebo treatment.

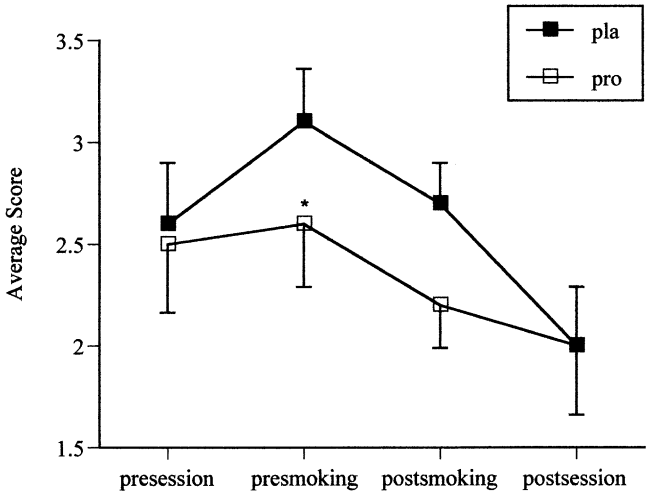

Fig. 3. The average (S.E.M.) rating of craving for cigarettes measured at the beginning of the session (presession), before (presmoking), and after (postsmoking) the sample smoking, and at the end of the session (postsession). * indicates significant treatment differences. The sample smoking occurred 2.5 h following 200 mg of oral progesterone or placebo treatment.

4. Discussion

The main finding of our study was that progesterone treatment given during the early follicular phase of the menstrual cycle was well tolerated and increased plasma progesterone levels to the range reached during the luteal phase of the menstrual cycle, between 3 and 30 ng/ml. In our study, subjects had low levels of estradiol and progesterone before the first and second sessions. Although there was a trend for increased estradiol levels before the second session, the difference was not significant and both estradiol levels were within the low end of the follicular phase range, 30–140 pg/ml. While our study focused on the acute effects of progesterone, in previous studies, estradiol and progestin treatment was given for 6 days during the early follicular phase of two consecutive menstrual cycle, without disrupting the menstrual cycle of women (Tan et al., 1996, 1997). This is important since both estradiol and progesterone treatment may lead to menstrual irregularities and withdrawal bleeding if given during the other phases of the menstrual cycle (Shangold et al., 1991). In our study, progesterone was well-tolerated and was not associated with menstrual irregularities, similar to previous reports. These results suggest that low and stable levels of endogenous estradiol and progesterone during the early follicular phase, compared to the other phases of the menstrual cycle, may minimize the risk of menstrual cycle disruption from sex

hormone treatment. Thus, the early follicular phase of the menstrual cycle is a useful period to investigate the short-term effects of exogenous progesterone in female smokers.

Our self-administration data revealed a diminished smoking behavior following progesterone treatment but the treatment effect did not reach statistical significance. The low smoking self-administration behavior under placebo condition limited the sensitivity of our model to detect decreases in smoking behavior. The token value used for puffs of cigarettes was probably higher than the optimum level. Interestingly, subjective ratings of craving and smoking behavior were parallel: both decreased under progesterone treatment. However, no progesterone treatment effects were observed for the overall severity of nicotine withdrawal symptoms. The duration of abstinence, approximately 12 h, was possibly too brief to investigate the medication effects on nicotine withdrawal symptoms, since these symptoms reach their peak 1–3 days after abstinence. Future studies with longer duration may be needed to investigate the effects of progesterone treatment on withdrawal symptoms and smoking behavior.

The subjective response to the sampling dose of cigarette showed a consistent trend for all the four items of DEQ, reaching significance for the rating of "good effects." These results suggest that progesterone treatment may attenuate the subjective effects from smoking. Our study did not address the subjective response to repeated cigarette smoking since subjects chose to take a low percentage of the optional doses that were available. The interaction between nicotine effects and progesterone has not been studied in humans. Some preclinical studies have shown that progesterone treatment may block the nicotinic receptors (Bertrand et al., 1991; Bullock et al., 1997; Uki et al., 1999; Valera et al., 1992), suggesting a possible mechanism for the attenuation of subjective effects from smoking by progesterone.

In our study, the tired subscale of POMS was increased under progesterone treatment. Among the most commonly reported side effects of progesterone treatment is sedation which may be due to stimulation of inhibitory GABA type A receptors by progesterone (Majewska, 1990; Majewska et al., 1986). Taking progesterone at night has been recommended to minimize the sedative effects of progesterone (de Lignieres, 1999). It is possible that these sedative-like effects of progesterone may have affected the smoking response of our subjects. Future studies, with careful examination of dose–response relationship of progesterone, may address this possibility.

This study has several limitations. First, only acute effects of a single dose size of progesterone were administered. Our goal was to reach the plasma progesterone levels found during the luteal phase of the menstrual cycle, which was achieved with a 200-mg dose. In future studies, using multiple doses of progesterone will be helpful to investigate dose-dependent effects of progesterone. Second, the treatment duration was brief, a single progesterone administration. Future studies with longer treatment durations will be needed to investigate the effects of progesterone in nicotine dependence. Third, our sample size estimates, which were based on differences in progesterone levels between two treatment groups, were probably too small to detect changes in smoking behavior using our model.

To summarize, these results suggest that early follicular phase of the menstrual cycle may be a useful interval to investigate the effects of exogenous progesterone in female smokers. Progesterone treatment was associated with attenuated subjective effects from smoking and a trend in decreased smoking behavior. The effect of progesterone for nicotine dependence in humans needs to be further studied.

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