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Progesterone improves cognitive performance and attenuates smoking urges in abstinent smokers

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Summary

Background—Progesterone, a steroid hormone, has been implicated in many CNS functions including reward, cognition, and neuroprotection. The goal of this study was to examine the dose-dependent effects of progesterone on cognitive performance, smoking urges, and smoking behavior in smokers.

Methods—Thirty female and thirty-four male smokers participated in a double-blind, placebo-controlled study. Female smokers were in the early follicular phase of their menstrual cycle during study participation. Smokers were randomly assigned to either 200 or 400 mg/day of progesterone or placebo, given in two separate doses, during clinic visit. The first 3 days of the treatment period, smokers abstained from smoking, which was verified with breath CO levels. Smokers attended an experimental session on day 4 where the number of cigarettes smoked were recorded starting two hours after the medication treatment.

Results—Progesterone treatment, 200 mg/day, significantly improved cognitive performance in the Stroop and the Digit Symbol Substitution Test. Progesterone at 400 mg/day was associated with reduced urges for smoking but did not change *ad lib* smoking behavior.

Conclusions—These findings suggest a potential therapeutic value of progesterone for smoking cessation.

Keywords

progesterone; cognitive performance; nicotine dependence; sex differences; menstrual cycle phase; sex differences

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1. Introduction

Progesterone is a steroid hormone synthesized in ovaries as well as in the adrenal glands. During the follicular phase of the menstrual cycle, women have low progesterone levels that are comparable to those in men (Pearson Murphy and Allison, 2000; Zumoff et al., 1990). In contrast, during the luteal phase of the menstrual cycle, and especially during pregnancy, women have higher progesterone levels than men (Chabbert Buffet et al., 1998). In the brain, progesterone binds to intracellular progesterone receptors found in the hypothalamus and many other brain regions (Brinton et al., 2008). Progesterone itself or through its active metabolites, allopregnanolone and pregnanolone, interact with many other receptors in the brain including the GABA_A, glycine, kainate, sigma1, and nicotinic receptors (Majewska et al., 1986) (Chesnoy-Marchais, 2009; Dar and Zinder, 1997; Romieu et al., 2003; Wu et al., 1998). In addition to its reproductive functions, progesterone and its active metabolites modulate several CNS functions, including reward, stress response, cognition and neuroprotection (Del Rio et al., 1998; Frye, 2007; Patchev et al., 1996) and likely contribute to sex and menstrual cycle influences on these CNS functions (Becker, 1999; Becker and Hu, 2008). Progesterone is under investigation for the treatment of cocaine addiction, seizure disorder, and traumatic brain injury (Evans and Foltin, 2006; Herzog, 2008; Sofuoglu et al., 2007; Stein, 2008).

Multiple studies have demonstrated the influence of sex and menstrual cycle phase on nicotine withdrawal severity, smoking behavior, and treatment outcomes (Carpenter et al., 2006; Perkins et al., 2000; Snively et al., 2000; Steinberg and Cherek, 1989). In a preliminary study aimed at better characterizing the contribution of progesterone in these sex and menstrual cycle influences, we evaluated progesterone's effects on cigarette smoking in female smokers (Sofuoglu et al., 2001). Progesterone treatment, compared to placebo, attenuated the subjective effects of the first cigarette and craving for cigarettes in overnight abstinent female smokers (Sofuoglu et al., 2001). Consistent with our findings, Allen and colleagues reported that among women trying to quit smoking, those who were assigned to quit during the follicular phase of their menstrual cycle relapsed faster to smoking than those who quit during the luteal phase (Allen et al., 2008). Since the luteal phase of the menstrual cycle is characterized by higher progesterone levels, these findings support the contribution of progesterone to smoking relapse and warrant further studies aiming to better characterize progesterone's role in smoking relapse.

The goal of this study was to determine the dose-dependent effects of progesterone treatment in male and female smokers using multiple outcomes including cognitive performance, smoking urges, and smoking behavior. Male and female smokers abstained from smoking for the first 3 days of the treatment period, followed by an experimental session on day 4. To our knowledge, this is the first study that has examined the dose-dependent effects of progesterone in male and female smokers for outcomes related to nicotine dependence. We hypothesized that progesterone treatment would dose-dependently reduce smoking urges and smoking behavior and enhance cognitive performance in abstinent smokers.

2. Methods

2.1. Participants

Thirty female and thirty-four male non-treatment-seeking smokers, between the ages of 18 to 45, were recruited from the New Haven area. Smokers had to have a history of smoking 10 to 25 cigarettes per day for at least a year and have a Fagerstrom Test of Nicotine Dependence (FTND) (Heatherton et al., 1991) score of 5 or higher. Subjects had to have normal physical, laboratory and psychiatric examinations. Subjects were excluded if they

had recent psychiatric diagnosis and treatment for Axis I disorders including major depression, bipolar affective disorder, schizophrenia, panic disorder, or currently dependent on or abusing alcohol or any drugs other than nicotine, as established by psychiatric examination (APA, 1994). Subjects had urine drug screening to rule out recent drug use. Women had to have regular menses, every 25 to 35 days; not be on oral contraceptives; and not be pregnant or nursing. Smokers were excluded if they were taking psychotropic medications (i.e., antidepressants, antipsychotics, or anxiolytics); using tobacco products other than cigarettes; or had allergies to progesterone or peanuts (peanut oil is the vehicle for micronized progesterone). The demographic and smoking characteristics of the subjects are shown in Table 1. Twelve additional subjects, 5 women and 7 men, were enrolled but dropped out of the study due to use of drugs of abuse (n=5), non-compliance with study procedures (n=3), or personal reasons (n=4). Experimental sessions were conducted at the VA Connecticut Healthcare System (West Haven campus). Subjects were paid for their participation and bonus payments were provided for refraining from smoking. This study was approved by the VA Connecticut Healthcare System Human Subjects Subcommittee and all subjects signed informed consent forms prior to their entry into the study. This study was registered at the Clinicaltrials.gov (NCT 00271206).

2.2. Procedures

This was a double-blind, placebo-controlled, between-subjects study that utilized a 2×3 factorial randomized group design: Sex (male or female) x medication (placebo, 200 mg or 400 mg/day of progesterone). Male and female smokers were randomly assigned to one of the three medication conditions: placebo, low dose (200 mg/day), high dose (400 mg/day) progesterone for four days. For women, the treatment was initiated within the first 3 days of the menstrual cycle, with day one being the first day of menses, and was completed within the early follicular phase (the first week from the beginning of the cycle). The early follicular phase is characterized by low and stable levels of endogenous estradiol and progesterone. Consequently, this timing minimizes the interaction between the endogenous sex hormones and progesterone treatment (Chabbert Buffet et al., 1998). Many previous studies have demonstrated the feasibility and safety of administering sex hormones to women during the early follicular phase of the menstrual cycle (Justice and de Wit, 2000; Sofuoglu et al., 2001; Sofuoglu et al., 2002). Subjects abstained from smoking beginning at 10 PM of day 1 of the treatment period until the morning of day 4. On days 2 and 3 of the treatment period, smokers had twice daily outpatient visits (morning and evening) that allowed for medication administration, monitoring of smoking behavior and collection of study measures. On day 4, subjects first received the morning dose of the assigned medication, progesterone or placebo. Two hours following the medication treatment, subjects smoked a cigarette of their own brand, followed by a 2-hour *ad lib* smoking where the number of cigarettes smoked was recorded. The *ad lib* smoking period was conducted in a ventilated room where subjects were monitored through a two-way mirror. For the *ad lib* period, smokers were instructed to smoke as they would normally do and were allowed to read magazines or listen to music but were not allowed to sleep. Subjects were provided their regular brand of cigarettes for the session. During the treatment period, abstinence from smoking was verified with alveolar carbon monoxide (< 10 parts-per-million; ppm). The study procedures are summarized in Table 2.

2.3. Progesterone administration

Micronized progesterone (Prometrium®) was obtained from Solvay Pharmaceuticals, Marietta, Georgia. Similar placebo capsules were prepared by the Pharmacy Services at the VA CT Healthcare System. After oral administration, 50–60% of micronized progesterone is absorbed. The recommended dose of progesterone for hormone replacement treatment is 200 to 400 mg/day, given as a single evening dose (PDR, 2009). In this study, 200 and 400

mg/day of progesterone were given in two divided morning and evening doses, except the first dose which was taken at 10 PM to minimize sedation. In a previous study with female smokers, a single dose of 200 mg oral progesterone achieved average plasma progesterone concentrations of 12.6 ng/ml (Sofuoglu et al., 2001), which is within the range of luteal phase levels, 2–20 ng/ml (de Lignieres, 1999). Because of the short half-life of micronized progesterone, the 200 mg dose was given twice daily to maintain stable plasma level of progesterone. Progesterone doses higher than 400 mg/day were not used since they are more likely to cause sedation.

2.4. Outcome measures

We obtained plasma progesterone and estradiol levels, heart rate and blood pressure, measures of smoking behavior, cognitive performance, and subjective measures during the course of this study. In addition, adverse events were recorded daily.

2.4.1. Plasma progesterone—Plasma progesterone levels were obtained on day 4 of treatment, just before and 2 hours after, in relation to progesterone and placebo administration. For women, plasma estradiol levels were obtained on day 4 at baseline.

2.4.2. Heart rate and blood pressure—Heart rate, systolic and diastolic blood pressure measurements were obtained daily.

2.4.3. Smoking behavior—These measures were alveolar carbon monoxide, saliva cotinine, and the number of cigarettes smoked. The alveolar CO and plasma cotinine concentrations were used to verify abstinence from smoking and level of smoking, respectively (Benowitz et al., 2002). Expired CO measurements were taken during each outpatient visit and before the experimental session. Plasma cotinine measurements were taken daily during outpatient visits. The number of cigarettes smoked during the *ad lib* smoking period on day 4.

2.4.4. Cognitive performance—The Digit Symbol Substitution Test (DSST) and the Stroop Interference Test were administered as indicators of cognitive functioning. The DSST measures sustained attention, response speed, and visuomotor coordination and is sensitive to nicotine deprivation (Eissenberg et al., 1996; Petrie and Deary, 1989). The task is to fill in blank spaces with the symbols that are paired with the number above the blank space as fast as possible for 90 sec. The main outcome measure for the DSST was the number of correct responses. The Stroop Interference Test, which measures response inhibition, is also sensitive to nicotine deprivation and nicotine replacement treatments (Mancuso et al., 1999; Provost and Woodward, 1991). We used a computerized Classical Stroop Test (Reeves, 2002), which is modeled after Golden's clinical version (Golden, 1978). Stimuli were presented in the colors red, blue, and green on a black background every 1 sec and had an interstimulus interval of 350 msec. The Stroop design consisted of one 3-minute block of congruent stimuli and one 3-minute block of incongruent stimuli. The main outcome measure for the Stroop test were throughput and interference score. While the throughput score reflects speed and accuracy (number of correct responses per minute), the interference score reflects slowing on the incongruent task relative to the congruent one (Reeves, 2002). The DSST was given before the initiation of treatment and on days 2, 3 and 4 of the treatment using different versions of the test. The Stroop was given before the initiation of treatment and on day 4 of treatment.

2.4.5. Self-report measures—Self-report measures included the Brief Questionnaire on Smoking Urges (BQSU), the Profile of Mood States (POMS), the Positive and Negative Affect Schedule (PANAS), and the Drug Effects Questionnaire (DEQ). The BQSU is a 10-

item scale that was originally developed by Tiffany and Drobes (Cox et al., 2001; Tiffany and Drobes, 1991). Smokers are asked how strongly they agree or disagree with items on a 7-point Likert scale. This scale has been found to be highly reliable and reflects levels of nicotine deprivation (Bell et al., 1999; Morgan et al., 1999). This scale has two factors: Factor 1 reflects an urge to smoke for stimulation and Factor 2 reflects an urge to smoke to relieve negative mood and withdrawal (Cox et al., 2001). The POMS is a 72-item rating scale used to measure the effects of medication treatments on mood (McNair et al., 1971). The POMS has six subscales: (1) composed-anxious; (2) agreeable-hostile; (3) elated-depressed; (4) confident-unsure; (5) energetic-tired; (6) clear headed-confused. The PANAS is a 20-item scale that assesses both negative and positive affective states (Watson et al., 1988). Smokers rate adjectives describing affective states on a scale of one to five using a specified time period (i.e., now, today, past week, etc.). This scale is sensitive to the affective symptoms of tobacco withdrawal (Kenford et al., 2002). These three scales were given daily during each morning outpatient visit. The DEQ, used to assess the acute subjective effects of smoking, consists of five items: “drug strength,” “good effects,” “bad effects,” “head rush” and “like the drug.” Subjects rated these items on a 100 mm scale, from 0 “not at all” to 100 “extremely.” The DEQ was given just after the subjects finished smoking during the experimental session. No adverse events were reported by participants during study participation.

2.5 Statistical analysis

To determine medication effects on outcome measures, we conducted a mixed-effect repeated-measures, between-subject analysis using the MIXED procedure in the Statistical Analysis System, Version 9.1.1. The model included a fixed main effect for medication (placebo, 200 or 400 mg progesterone), sex (male or female), time, and interaction terms for medication-by-time, and medication-by-sex. Baseline values for outcome measures, before the initiation of medication, were included as covariates in the respective analyses. For the analysis of cognitive performance data, where there was interindividual variation, change scores were used in the analyses. For each analysis, significant main effects for medication, sex, medication, or sex-by-medication interactions ($p < 0.05$) were followed by post-hoc group comparisons using Dunnett’s two-tailed t-test. When sex-by-medication interaction effects were significant, the three medication groups were compared separately for males and females.

3. Results

3.1 Demographics

Participant demographic characteristics are presented in Table 1. There were no significant group or sex differences for basic demographic and smoking variables.

3.2 Progesterone and estradiol levels

Plasma progesterone levels are presented in Figure 1. For peak plasma progesterone levels, as expected there was a significant main effect for medication [$F(2, 56) = 19.7$; $p < 0.0001$]. *Post hoc* comparisons indicated that both 200 and 400 mg progesterone led to higher plasma levels than placebo levels. The 400 mg progesterone condition was associated with significantly higher plasma levels than the 200 mg progesterone treatment. For women, baseline estradiol levels on day 4 were 47 (7), 49 (5) and 49 (8) pg/mL under placebo, 200 mg progesterone, and 400 mg progesterone treatment, respectively. These estradiol levels are consistent with the plasma estradiol levels found in the follicular phase of the menstrual cycle (de Lignieres and Silberstein, 2000).

3.3 Heart rate and blood pressure

For daily heart rate measurements (see Figure 2), there was a significant sex-by-medication interaction [$F(2, 56.7) = 10.06; p < 0.001$], with lower heart rate values in the 400 mg or 200 mg progesterone group as compared to placebo in males. For diastolic blood pressure, a similar sex-by-medication interaction was observed [$F(2, 58.3) = 3.9; p < 0.05$]. In women, the average diastolic blood pressure for the 400 mg progesterone group was significantly lower than that for the placebo group ($p < 0.05$).

3.4 Smoking behavior

As expected, saliva cotinine levels decreased over the protocol duration [$F(2, 119) = 15.3; p < 0.0001$]. The mean (SE) values of saliva cotinine on the first and the fourth day of the study were 168 (17) and 103 (13), respectively. There was no medication effect on saliva cotinine [$F(2, 57.1) = 0.6; ns$]. The number of CO measurements over 10 ppm, indicating recent smoking were 12 (10%) for the 400 mg progesterone, 14 (11%) for the 200 mg progesterone, and 16 (13%) for placebo groups [$\chi^2(2, N=377; ns)$].

There was no medication effect in terms of the number of cigarettes smoked during *ad lib* smoking [$F(2, 54) = 0.1; ns$]. The average number of cigarettes smoked (SE) during the 2-hour smoking session were 3.3 (0.5), 2.9 (0.5) and 3.1 (0.4) for the placebo, 200 and 400 mg progesterone conditions, respectively.

3.5 Cognitive performance

For the number of correct responses in the DSST (see Figure 3), there was a significant main effect for medication condition, [$F(2, 59) = 3.3; p < 0.05$], with higher scores in the 200 mg progesterone group, when compared to the placebo or the 400 mg progesterone group ($p < 0.05$).

For the throughput score (number of correct items in one minute) on the Stroop test (see Figure 3), there was a significant effect for sex-by-medication interaction [$F(2, 50.4) = 3.1; p < 0.05$]. Pairwise comparisons indicated that for the 200 mg progesterone scores were significantly higher than for the placebo medication group among women. The interference score did not show significant medication or sex differences.

3.6 Self-report measures

For the POMS or PANAS, no significant main effects for medication, sex or interaction were found.

For the factor I of BQSU (Figure 4), there was a significant treatment-by-time interaction [$F(6, 180) = 2.2; p < 0.05$]. Pairwise comparisons indicated that the factor I score for the 400 mg progesterone group was significantly lower than the placebo and 200 mg progesterone groups on day 4 ($p < 0.05$).

In terms of the subjective responses to sample smoking, assessed in the *ad lib* session with DEQ (Figure 4), there was a significant main effect of medication for drug strength, [$F(2, 58) = 4.3; p < 0.05$], with higher ratings in the placebo group compared to the 200 or 400 mg progesterone group. For drug liking, there was a significant main effect for medication [$F(2, 58) = 3.5; p < 0.05$], with lower ratings in the 200 mg progesterone condition, compared to the placebo or 400 mg progesterone conditions. Other DEQ items did not show significant medication effects.

4. Discussion

The main findings of this study were that progesterone treatment reduced urges to smoke in abstinent smokers but did not change *ad lib* smoking behavior. While progesterone treatment improved cognitive performance in the Digit Symbol Substitution Test in both male and **female** abstinent smokers, only females showed improvement in the Stroop task performance. While the 400 mg/day progesterone dose was more effective in reducing urges to smoke, the 200 mg progesterone dose was more effective in improving cognitive performance. These findings partially support our study hypotheses regarding progesterone effects in smokers. The main findings of the study are discussed further below.

Progesterone treatment reduced urges for smoking in abstinent smokers as indexed by Factor 1 (urge to smoke for stimulation) of the BQSU. This effect was only seen in the 400 mg progesterone group. Similar to these findings, in a previous study, we reported that progesterone treatment was associated with decreases in craving for cigarettes in female smokers (Sofuoglu et al., 2001). Progesterone also modulated the self-report ratings of sample smoking following a 3-day abstinence from smoking. While the 200 and 400 mg/day attenuated the self-report rating of drug strength, the 200 mg/day progesterone attenuated the rating of “drug liking.” No treatment effects were observed for the rating of other items. Consistent with these findings, in previous studies progesterone treatment attenuated some of the subjective effects of smoking (Sofuoglu et al., 2001) or intravenous nicotine administration in smokers (Sofuoglu et al., 2009). Progesterone’s effects are not specific to nicotine. In both preclinical and clinical studies, progesterone has been shown to attenuate cocaine reward (Anker et al., 2007; Evans and Foltin, 2006; Feltenstein et al., 2009; Russo et al., 2008; Sofuoglu et al., 2002; Sofuoglu et al., 2004). As mentioned before, progesterone is being examined as a potential treatment medication for cocaine addiction.

In spite of reduced urges for smoking, smokers receiving progesterone treatment did not change their smoking behavior. Abstinence rates from smoking during the treatment phase, verified with CO and cotinine levels, were similar for all treatment groups. Similarly, the number of cigarettes smoked in the *ad lib* smoking period did not differ significantly. One contributing factor to our finding might be lack of sensitivity of *ad lib* smoking paradigms to changes in smoking behavior. More recently, a choice procedure, where money is used as an alternative reinforcer to smoking, has been shown to enhance the sensitivity of laboratory models to detect medication effects on smoking behavior (Bisaga et al., 2007; Rohsenow et al., 2008). In addition, our sample was comprised of non-treatment seeking smokers who may be less responsive to pharmacological interventions for reducing smoking (Tidey and Rohsenow, 2009). It will be important to examine progesterone’s effects on smoking behavior in smokers interested in quitting smoking.

Progesterone treatment enhanced the number of correct responses in the Stroop and the DSST in abstinent smokers. Progesterone’s effects on the Stroop performance, but not on the DSST performance, were sex specific: only women showed improvement. Consistent with our findings, in preclinical studies progesterone treatment enhanced learning and memory in hippocampal and prefrontal tasks in aged male and female ovariectomized mice (Frye and Walf, 2008a; Frye and Walf, 2008b). Progesterone’s cognitive effects were selective for the task and dependent on the timing of injection in relation to the tasks. In a recent study, 10 or 20 mg/kg progesterone enhanced object recognition, but not performance on a spatial recognition task in female mice (Harburger et al., 2008). In contrast, progesterone’s effects on cognitive functioning have been less consistent in humans. In normally cycling women, selective cognitive functions including verbal memory, attention, and visual memory were enhanced during the luteal phase of the menstrual cycle and performance in these functions were positively correlated with endogenous progesterone levels (Phillips and Sherwin, 1992;

Solis-Ortiz and Corsi-Cabrera, 2008). However, when administered directly, progesterone did not affect or reduce cognitive performance in healthy males (Gron et al., 1997), normally cycling females (van Wingen et al., 2007) or postmenopausal females (Schussler et al., 2008). Moreover, the Women's Health Initiative recently reported little or no benefit of estradiol plus progestins (medroxyprogesterone acetate) on global cognitive function and memory function in postmenopausal women (Rapp et al., 2003; Resnick et al., 2006). These findings clearly raised further questions regarding the specific effects of progesterone on cognitive function and how these effects are moderated by variables such as age, baseline cognitive functioning, concomitant estradiol treatment and type of progestin (progesterone vs. medroxyprogesterone) (Henderson, 2008; Maki, 2005; Pazol et al., 2009).

Our findings differ from previous reports observations regarding progesterone's effects on cognitive performance. These differences may have, in part, resulted from some unique features of our study design. First, we chose micronized progesterone rather than synthetic progestins, which are commonly used in oral contraceptives. For example, the Women's Health Initiative Studies cited above used medroxyprogesterone, which differs significantly from progesterone in its pharmacological effects, including lack of neuronal protection or GABA_A receptor activation (Hermsmeyer et al., 2008; Jodhka et al., 2009; Pazol et al., 2009). Many authors have cautioned against not generalizing findings obtained with MPA or other progestins to progesterone (Hermsmeyer et al., 2008). Second, while many previous human studies used a single dose of progesterone, we used two different doses of progesterone which allowed enhanced cognitive performance with the 200 mg but not the 400 mg dose of progesterone. Since progesterone is known to have sedative effects, one possible explanation was greater sedation with the 400 mg dose than the 200 mg progesterone dose which might have reduced the cognitive performance. However, subjects did not report greater sedation under 400 mg progesterone. Third, in our study smokers were tested during smoking abstinence, which is associated with reduced cognitive functioning, providing greater room for improvement in performance. Lastly, female smokers in our study were normally cycling women. It has been suggested that progesterone shows less beneficial effects in post-menopausal women possibly due to long standing low baseline progesterone levels (Lewis et al., 2008; Maki, 2005).

An important question is what mechanisms mediate these cognitive and subjective effects of progesterone in smokers? The positive modulatory effects of progesterone metabolites, especially allopregnanolone, on the GABA_A receptors have been proposed to attenuate drug reward, although other mechanisms may also play a role (Anker et al., 2009; Callachan et al., 1987; Finn et al., 2010; Ford et al., 2005; Majewska, 1990; Smith et al., 2009). For example, progesterone itself is allosteric inhibitors at nicotinic receptors, including the neuronal $\alpha 4 \beta 2$ subtype (Bullock et al., 1997; Dar and Zinder, 1997; Paradiso et al., 2000). However, it remains to be determined whether progesterone at physiological concentration affects nicotinic receptor function. Progesterone also facilitates synaptic plasticity through its effects on intracellular signaling, synaptic proteins, and spine density in the hippocampus (Choi et al., 2003; Nilsen and Brinton, 2003; Woolley and McEwen, 1993). These synaptic effects may possibly contribute to the cognitive enhancement seen with progesterone.

Progesterone treatment was well-tolerated by both male and female smokers and did not have any adverse effects on mood assessed with the PANAS and POMS. Although progestins have been associated with depressed mood (Girdler et al., 1999; Sherwin, 1994), carefully conducted studies have not confirmed these findings (Cummings and Brizendine, 2002). Progesterone had modest effects on blood pressure and heart rate measurements: it reduced heart rate in males and reduced diastolic blood pressure in females. Progesterone's attenuation of diastolic blood pressure and heart rate is consistent with both preclinical and clinical studies. In a previous study, progesterone treatment lowered diastolic blood pressure

in hypertensive men and postmenopausal women (Rylance et al., 1985). Blood pressure and heart decreases may be mediated by attenuated sympathetic system activity since progesterone (400 mg/day) has been shown to decrease venous norepinephrine levels in normotensive men (Tollan et al., 1993). In contrast to progesterone, cigarette smoking is known to increase blood pressure by increasing activity of the sympathetic nervous system (Benowitz and Gourlay, 1997).

These findings may have important clinical implications for potential use of progesterone in smoking cessation. First, improvement of cognitive performance and attenuation of smoking urges and subjective effects from smoking by progesterone may point to potential therapeutic value for smoking cessation. Smokers trying to quit experience reduced cognitive function, and improvement of cognitive function has been proposed as one of the treatment targets for more effective smoking cessation pharmacotherapies. Further, the first few cigarette puffs following abstinence is regarded to be highly rewarding and linked to relapse in smokers trying to quit (Brandon et al., 1990; Kenford et al., 1994). Attenuation of the subjective effects of the first cigarette with progesterone supports its potential use in preventing relapse in abstinent smokers. Importantly, the cognitive-enhancing effects of progesterone were much more prominent in female smokers than males. In general, women have been found to be less responsive to smoking cessation treatments than men (Cepeda-Benito et al., 2004; Scharf and Shiffman, 2004). Thus, there is a great need to develop more effective treatments for female smokers. This is also true for postpartum smokers. While approximately half of the women who smoke before pregnancy are able to quit smoking during pregnancy, 40 to 52 % relapse within 2 weeks and 70 to 80 % resume smoking within a year of childbirth (Colman and Joyce, 2003). Given that following childbirth there is a significant drop in progesterone levels (McCoy et al., 2003) coinciding with high rates of relapse to smoking, progesterone hormone may have a therapeutic use to prevent smoking relapse in postpartum women.

To conclude, in abstinent smokers progesterone at 200 but not 400 mg improved cognitive performance in the Stroop and DSST. Progesterone treatment also attenuated urges for smoking and some of the subjective effects from smoking. Progesterone treatment may have therapeutic value for smoking cessation especially in female smokers. Further clinical studies examining the utility of progesterone treatment for smoking cessation are warranted.

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Figure 1.

The average (with standard error of the mean-SEM) plasma progesterone levels (ng/ml) for the 400 mg and 200 mg progesterone and placebo treatments. The measurements were taken just before and 2 hours after administration of progesterone or placebo treatment on day 4.

*indicates significant differences from placebo ($p < 0.05$). See text for details.

Figure 2.

The average (with SEM) heart rate for the 400 mg or 200 mg progesterone or placebo treatment conditions in male and female smokers. Measurements were taken daily during the 4-day treatment period. *indicates significant differences from placebo ($p < 0.05$). See text for details.

Figure 3.

The average (with SEM) throughput score for the Stroop and the DSST correct items for the 400 mg or 200 mg progesterone or placebo conditions. Bars represent the changes from baseline. Measurements were taken at baseline and on day 4 for the Stroop and on days 2, 3, and 4 for the DSST. # indicates significant main effect for treatment and * indicates significant differences from placebo ($p < 0.05$). See text for details.

Figure 4.

The average (with SEM) Factor 1 scores of the BQSU for the 400 mg, or 200 mg progesterone, or placebo conditions in males and female smokers. Measurements were taken daily during the 4-day treatment period. # indicates significant treatment-by-time interaction ($p < 0.05$). See text for details.

Figure 5.

The average (with SEM) ratings of subjective responses to sample smoking measured with the Drug Effects Questionnaire (DEQ) under 400 mg or 200 mg progesterone or placebo conditions. The measurements were obtained after smoking a cigarette. # indicates significant main effect for treatment ($p < 0.05$). See text for details.

Table 1

Comparison of medication groups for demographics and smoking characteristics

	Progesterone 400 mg/day (n=22)				Progesterone 200 mg/day (n=21)				Placebo (n=21)				P-values
	N		%	N		%	N		N		%		
Race													
Caucasian	5		23	8		38	6		29		0.5		
African-American	15		68	12		57	14		67				
	Mean		SD	Mean		SD	Mean		SD				
Age	31.5		8.2	35.8		8.6	34.6		9.0		0.3		
Years of smoking	15.0		7.6	20.2		7.5	16.1		10.0		0.15		
Cigarettes smoked/day	15.3		4.8	17.4		6.1	17.4		5.8		0.3		
FTND score	5.2		1.6	5.5		2.3	5.5		1.7		0.8		
Plasma cotinine values	127		140	157		158	146		103		0.7		

Table 2

Study Procedures

Study Day	Time	Event
Day 1	10 PM	First dose of the medication Start smoking abstinence
Days 2 and 3	8AM	Morning visit for medication and assessments
	4 PM	Evening visit for medication and assessments
Day 4	8AM	Morning medication Blood draw for baseline progesterone
	10 AM	Blood draw Ad lib smoking start
	Noon	End of ad lib session