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Subjective Response to Nicotine by Menstrual Phase

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Abstract

Introduction—The luteal menstrual phase might be a favorable time for smoking cessation when non-nicotine interventions (e.g. counseling, bupropion) are used, whereas the follicular menstrual phase appears favorable when nicotine interventions are used. Thus, there may be an interaction between menstrual phase and response to nicotine. We sought to examine the role of menstrual phase on response to nicotine during acute smoking abstinence.

Methods—In this controlled cross-over trial, women completed two identical experimental sessions (follicular [F] vs. luteal [L] phase) after four days of biochemically-verified smoking

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Contributors
Alicia Allen completed the literature review, participated in protocol development and wrote the first draft of the manuscript. Scott Lunos conducted the statistical analysis. Stephen Heishman provided expertise on the measurement and interpretation of nicotine response measurements. Mustafa al'Absi and Dorothy Hatsukami were co-investigators on the project. Sharon Allen was the principle investigator on the project. All authors participated in interpretation of data, as well as writing, editing and approval of the final manuscript.

Conflict of Interest
All authors declare that they have no conflict of interest.

abstinence. During the sessions, nicotine nasal spray was administered, and participants provided a series of subjective assessments.

Results—Participants (n=140) were 29.7±6.6 years old and smoked 12.6±5.8 cigarettes per day. Compared to the F phase, the L phase was associated with a greater increase in stimulation (7.2±2.2 vs. 14.4±2.3, p=0.01, respectively) and greater decrease in urge to smoke (−13.6±2.3 vs. −21.1±2.5, p=0.02, respectively) after the first dose of nicotine. No other significant differences were observed.

Conclusions—Out of 13 total measures examined at two different time points, we observed only two significant menstrual phase differences in the subjective response to nicotine. Therefore, these data do not provide strong evidence for a menstrual phase difference in the subjective response to nicotine. Additional research is needed to confirm this relationship and explore how non-nicotine smoking reinforcements (such as sensory sensations) may vary by menstrual phase.

Keywords

Addiction; Nicotine; Menstrual Cycle; Smoking; Hormones

1. Introduction

Women relapse to smoking at different rates and for different reasons compared to men (CDC, 2012; Nakajima & al'Absi, 2012; Perkins, 2001). Although research indicates women smoke more for non-nicotine reinforcers such as sensory effects and weight control (Perkins, 2001), women smokers are more sensitive to the effects of nicotine than men. Many studies using various forms of nicotine (nasal spray, oral, transdermal patch, and intravenous) have demonstrated that women have a greater subjective and physiological response to nicotine (Evans, Blank, Sams, Weaver, & Eissenberg, 2006; Myers, Taylor, Moolchan, & Heishman, 2008; Netter, Müller, Neumann, & Kamradik, 1994; Sofuoglu & Mooney, 2009). DeVito and colleagues, however, noted that men displayed a greater subjective response to intravenous nicotine, whereas women displayed a greater physiological response (DeVito, Herman, Waters, Valentine, & Sofuoglu, 2014). Thus, sex hormones might play a role in response to nicotine.

Recent research has examined the role of menstrual phase (as a proxy for sex hormones) in smoking behavior and cessation (for additional information see the following review articles: Carpenter, Upadhyaya, LaRowe, Saladin, & Brady, 2006; Lynch & Sofuoglu, 2010). Overall, the follicular phase (low progesterone/estradiol [PE] ratio) seems favorable for smoking cessation when nicotine replacement therapy (NRT) is used (Carpenter, Saladin, Leinbach, Larowe, & Upadhyaya, 2008; Franklin et al., 2008). However, in the absence of NRT, the luteal phase (high PE ratio) may lead to more favorable outcomes (S. S. Allen, Bade, Center, Finstad, & Hatsukami, 2008; Mazure, Toll, McKee, Wu, & O'Malley, 2011). The specific mechanisms involved are unknown, but may be related to the biological response to nicotine at varying levels of sex hormones (Franklin & Allen, 2009). Understanding the effect of menstrual phase and sex hormones on response to nicotine will allow for the development of smoking cessation interventions tailored to the specific needs of premenopausal women.

Although individual differences in the subjective nicotine response have not been well studied, they are likely associated with the reinforcing effects of smoking (Stolerman & Jarvis, 1995). While it remains unknown as to whether subjective response may serve as an indicator of risk for smoking relapse (Pillitteri, Kozlowski, Sweeney, & Heatherton, 1997; Pomerleau, 1995), limited new research has begun exploring the effect of menstrual phase on nicotine response. Subjective nicotine response was greater during the follicular phase compared to the luteal phase in female smokers after overnight abstinence (DeVito et al., 2014). However, this relationship has not been examined in women who were abstinent for greater than 12 hours. The aim of this project was to determine if menstrual phase influenced the subjective response to nicotine during acute smoking abstinence. We hypothesized that the subjective response to nicotine would be greater in follicular compared to luteal phase.

2. Methods

2.1 Study Sample

A sample of women were recruited for a study designed to explore the differences in smoking-related symptomatology by menstrual phase and depressive symptoms (S. S. Allen et al., 2014). Inclusion criteria included women between the ages of 18 and 40, smoking at least five cigarettes per day for at least the past year, regular menstrual cycles for at least the past six months, and stable physical and mental health. Exclusion criteria were recent (<3 months) pregnancy or breastfeeding, current premenstrual dysphoric disorder (PMDD), current major depressive disorder, and use of exogenous hormones (including hormonal contraceptives), psychotropic medication or any other forms of nicotine or smoking cessation aids.

2.2 Study Procedures

All study procedures were approved by the Human Subject Protection Program at the University of Minnesota. To assess eligibility criteria, participants completed a telephone interview followed by an in-person screening visit, where informed consent was obtained and collection of baseline data was completed (e.g. demographics and smoking behavior including nicotine dependence via the Fagerstrom Test of Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991)). After study enrollment, participants were randomly assigned to complete the first testing week in Follicular (F; menstrual cycle days 2–7, with day 1 defined as the onset of menses) phase followed by the Luteal (L; 3–8 days after ovulation as determined by urine luteinizing hormone tests) phase, or vice versa. Serum hormone levels (progesterone and estradiol) were measured allowing for retrospective confirmation of menstrual phase. Additional detailed information on screening, randomization and protocol have been published elsewhere (S. S. Allen et al., 2014).

Each testing week consisted of two days of ad libitum smoking, followed by four days of smoking abstinence. During this six-day testing period, participants attended daily clinic visits to confirm smoking status (expired carbon monoxide < 5 ppm and salivary cotinine < 15 ng/mL on fourth day of smoking abstinence) (Benowitz, Bernert, Caraballo, Holiday, & Wang, 2009). On Day 6 (fourth day of smoking abstinence), participants completed a

nicotine exposure laboratory session. During the session, participants were administered nicotine nasal spray (Nicotrol 2mg) at Time 0 and 90 minutes, with assessment of subjective response measures at Time −30, 5, 10, 20, 30, 60, 95, 100, 110 and 120 minutes. Subjective response was assessed using two measures: (1) Subjective State Scale (SSS) (al'Absi, Hatsukami, & Davis, 2005; al'Absi, Hatsukami, Davis, & Wittmers, 2004) that contains 24-items yielding five subscales: Negative Affect, Positive Affect, Physical Symptoms (e.g. headache, hungry), Withdrawal and Craving, and (2) Visual Analog Scale (VAS) items that measured potentially rapid changes in negative or positive drug effects: *alert*, *dizzy*, *head rush*, *jittery*, *pleasant*, *relaxed*, *stimulated*, and *urge to smoke*. Participants responded on a 100-mm line ranging from 'not at all' to 'very much' (Jones, Garrett, & Griffiths, 1999). Blood pressure and heart rate were also measured at each time point to document physiological responses to nicotine (S. S. Allen et al., 2013). At the completion of this laboratory session, participants resumed ad libitum smoking for approximately six weeks (1.5 menstrual cycles; a median of 46 days) and then completed identical data collection procedures in the alternate menstrual phase. Participants were compensated with cash (up to $910) for their time and efforts.

2.3 Statistical Analyses

Descriptive statistics were calculated for demographics and baseline characteristics. Nicotine response was defined as the change from baseline (Time −30 minutes) to the first time point (Time 5 minutes) after the nicotine dose. Random-intercept models, adjusting for study design factors and potential confounders (e.g. sequence (carry-over), time effects, and depressive symptoms), were used to investigate the association of menstrual phase with nicotine response. Similar models were used to compare baseline measures. P-values less than 0.05 were deemed statistically significant. SAS V9.3 (SAS Institute, Cary, NC) was used for the analyses.

3. Results

3.1 Study Sample

A total of 208 women were enrolled into the study. Of those, 61 participants were excluded from the analyses due to participant discontinuing study participation (n=51), inability to achieve smoking abstinence (n=11) or having hormone levels that were not consistent with menstrual phase of testing (n=6). Therefore, the final sample size for this analysis was 140, including 72 who were randomized to the F-L order and 68 randomized to L-F order. Overall, women were 29.7 (S.D. ± 6.6) years old and smoked 12.6 (S.D. ± 5.8) cigarettes/day. Most (93%) had at least a high school education and were non-Hispanic White (54%) or Black (24%). Participants who were White non-Hispanic were more likely to be randomized to L-F phase testing order (p=0.04), whereas participants who were Black non-Hispanic were more likely to be randomized to the F-L testing order (p=0.02). There were no other statistically significant differences in study participants based by randomization (F-L vs. L-F) or by completion status (discontinued/excluded vs. completed).

3.2 Effect of Menstrual Phase on Subjective Response to Nicotine

Two significant differences in the subjective response to nicotine by menstrual phase were noted after the first dose of nicotine nasal spray (Table 1). First, the L phase was associated with a greater increase in the VAS item *stimulated* compared to the F phase (14.4±2.3 vs. 7.2±2.2, p=0.01; respectively). Second, the L phase was associated with a greater reduction in the VAS item *urge to smoke* than the F phase (−21.1±2.5 vs. −13.6±2.3, p=0.02; respectively). There were no significant menstrual phase differences in subjective response to nicotine after the second dose of nasal spray was administered.

4. Discussion

The aim of this controlled, cross-over trial was to examine the differences in subjective response to nicotine by menstrual phase during acute smoking abstinence. We found that after the first dose of nicotine nasal spray, the luteal phase was associated with a greater increase in *stimulated* (as indicator of acute spray response) and a greater decrease in *urge to smoke* (an indicator of abstinence relief). However, the majority of the associations explored were null, providing little evidence for a difference in nicotine sensitivity by menstrual phase after four days of biochemically verified smoking abstinence. This is in contrast to a recently published study that administered intravenous nicotine after overnight abstinence and observed that women in the luteal phase, compared to women in the follicular phase, had a blunted decrease in craving. (DeVito et al., 2014) Differences in observations may be related to the delivery of nicotine (e.g. nasal spray versus intravenous) or length of abstinence period (e.g. four-days versus overnight).

There are several possible explanations for the lack of observed menstrual phase differences in subjective response to nicotine. First, given the nasal mucosal changes over the course of the menstrual cycle, (Taylor, 1961) there may have been a difference in the nicotine absorption by menstrual phase, resulting in a differential effect of the nicotine nasal spray on subjective symptoms. However, as noted in our recent publication, we observed significantly *less* nicotine absorption in the luteal phase (S. S. Allen et al., 2013). This conflicts with our observations in the present paper where we observed a *greater* subjective response during the luteal phase. A second possible explanation could be the change in sex hormones within each menstrual phase. Menstrual phase is an imperfect proxy for sex hormones, given their constant fluctuation. Recently, Schiller and colleagues concluded that the progesterone to estradiol ratio, rather than progesterone or estradiol alone, was the best hormonal predictor of smoking behavior (Schiller, Saladin, Gray, Hartwell, & Carpenter, 2012). Therefore, in ad hoc analyses we explored the association between the PE ratio and our outcomes of interest (data not shown). Only one significant association was noted between PE ratio and *stimulation* (β=83.3 (SE=25.5), p=0.001). This suggests that the greater stimulation observed in the luteal phase may have been driven by the PE ratio, but overall provides little evidence for an association between PE ratio and subjective response to nicotine. A third possible explanation may be related to differential withdrawal symptoms by menstrual phase. Previous research has indicated that withdrawal symptoms may be worse in the luteal phase (A. M. Allen, Allen, Lunos, & Pomerleau, 2010; Carpenter et al., 2006). It is plausible that more severe withdrawal symptoms may be associated with greater

subjective response to nicotine. Thus, we examined the association between withdrawal symptomatology (withdrawal, craving and urge to smoke) and subjective response to nicotine (data not shown); no significant associations were observed. Therefore, this is not likely the explanation for our observations. Finally, it is possible the two significant differences we observed were due to chance. With an alpha level set at 0.05 and a total of 26 statistical tests conducted, we would expect to observe 1–2 significant differences due to chance alone. Overall, our results do not provide evidence for a menstrual phase difference in the subjective response to nicotine. Given that women are more responsive to the non-nicotine factors associated with smoking (e.g., cue response, weight control) and also have improved cessation outcomes with non-nicotine medications, (A. M. Allen, Hatsukami, & Oncken, 2013; Perkins, 2001) additional research is needed to explore how non-nicotine reinforcements (e.g. sensory sensations, mood stabilization) may vary by menstrual phase.

This study has several limitations. First, a large proportion (33%) of participants either discontinued the study or were excluded from the analysis, and this likely introduced selection bias. Third, study staff and participants were not blinded to menstrual phase of testing and open-label nicotine nasal spray was used. The lack of blinding may have induced biases into our results. Despite these limitations, this study has several strengths including the controlled cross-over design, which limits confounding, and detailed measurement of menstrual phase, smoking status and response to nicotine.

In conclusion, we observed only two significant differences in the subjective response to nicotine by menstrual phase and the majority of our observations were null. Thus, contrary to our hypotheses, subjective response to nicotine after four days of smoking abstinence may not vary menstrual phase. Additional research is needed to confirm these findings and explore how non-nicotine reinforcements may vary by menstrual phase.

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Highlights

- A cross-over study was used to explore nicotine response by menstrual phase.
- Luteal phase had greater changes in stimulation and urge to smoke.
- However, most menstrual phase differences were null.
- Subjective response to nicotine may not vary by menstrual phase.

Table 1

Subjective Response (Mean ± Standard Error) to Nicotine Nasal Spray during Acute Smoking Abstinence by Menstrual Phase (n=140)

	−30 Minutes			+ 5 minutes			+95 minutes		
	F Phase	**L Phase**	**p-value**	**F Phase**	**L Phase**	**p-value***	**F Phase**	**L Phase**	**p-value****
Acute Spray Responses									
Stimulated	50.5 (2.5)	47.6 (2.6)	0.2145	58.5 (2.3)	61.9 (2.4)	0.0111	56.6 (2.3)	61.0 (2.5)	0.5415
Head Rush	11.1 (1.7)	9.7 (1.8)	0.5133	34.9 (2.9)	36.2 (3.1)	0.4328	34.8 (2.9)	32.6 (3.1)	0.2308
Jittery	20.3 (2.6)	22.9 (2.8	0.4167	29.4 (2.6)	33.1 (2.8)	0.7791	28.3 (2.7)	34.5 (2.9)	0.7580
Dizzy[1]	8.7 (1.6)	9.9 (1.7)	0.5226	25.8 (2.6)	24.3 (2.7)	0.3665	22.4 (2.5)	22.1 (2.6)	0.7157
Alert	64.9 (2.1)	62.0 (2.3)	0.1814	66.8 (1.9)	66.2 (2.0)	0.4754	67.3 (2.0)	66.2 (2.1)	0.7325
Physical Symptoms[2]	4.3 (0.4)	4.7 (0.5)	0.3285	4.5 (0.4)	5.0 (0.4)	0.7441	6.1 (0.4)	6.3 (0.4)	0.3747
Abstinence Relief									
Urge to Smoke	64.4 (2.8)	68.6 (3.0)	0.1933	51.2 (3.1)	48.1 (3.3)	0.0167	47.3 (3.0)	46.3 (3.2)	0.3982
Craving[3]	4.0 (0.2)	3.9 (0.2)	0.5194	3.3 (0.2)	3.2 (0.2)	0.5510	2.9 (0.2)	2.9 (0.2)	0.5576
Withdrawal	10.1 (0.6)	9.5 (0.6)	0.3115	7.9 (0.5)	8.0 (0.5)	0.1326	7.7 (0.5)	8.5 (0.6)	0.1018
Affect									
Relaxed	58.6 (2.6)	60.9 (2.5)	0.3819	61.3 (2.1)	62.5 (2.2)	0.7179	63.6 (2.2)	64.1 (2.3)	0.8713
Pleasant	64.8 (2.2)	64.2 (2.4)	0.8241	64.4 (2.1)	63.4 (2.2)	0.8535	65.3 (2.1)	65.0 (2.3)	0.6734
Positive Affect	19.2 (0.8)	19.8 (0.8)	0.3623	19.8 (0.8)	20.2 (0.8)	0.9340	20.1 (0.8)	20.0 (0.8)	0.2344
Negative Affect	6.9 (0.5)	6.7 (0.6)	0.8051	5.2 (0.5)	5.5 (0.5)	0.5641	5.9 (0.5)	6.8 (0.5)	0.1869

*Difference was assessed by the change in pre-nicotine administration value (−30) subtracted from the post-nicotine administration peak value (5 minutes).

**Difference was assessed by the change in post administration peak value (5 minutes) subtracted from the post second dose administration (95 minutes).

[1]Testing Period Effect: Week 1 < Week 2; p=0.0167;

[2]Period Effect: Week 1 > Week 2; p=0.0037;

[3]Order Effect: p=0.0056 [Looking at only Week 1: F Phase > L Phase, −0.8 (0.2) vs −0.0 (0.2), respectively, diff=−0.7 (0.3) p=0.0145]