

Brief report

Retrospective study: Influence of menstrual cycle on cue-induced cigarette craving

**Teresa R. Franklin, Kimberly Napier, Ronald Ehrman, Peter Gariti,
Charles P. O'Brien, Anna Rose Childress**

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Cigarettes acquire reinforcing properties from nicotine and from cues associated with their intake. However, smoking in males and females may be reinforced differentially. Smoking in females is posited to be influenced more by cues whereas male smoking is influenced predominantly by the direct pharmacological actions of nicotine in the brain. Menstrual cycle phase may contribute to some of the sex differences observed in smokers. We hypothesized that females may report more intense craving to smoking cue exposure than males and, further, that female craving scores may be influenced by menstrual cycle phase. Thus, we reexamined previously collected cue exposure data with respect to sex and cycle phase. Self-report measures were collected from subjects prior to and immediately following exposure to visual smoking stimuli. The study included 69 male and 41 female treatment-seeking subjects who smoked more than 15 cigarettes per day for more than 10 years. Females were grouped according to cycle phase. Of the female subjects, 17 were classified as follicular phase females (FFemales) and 24 were classified as luteal phase females (LFemales). Change scores were calculated from the subjective data collected before and after stimulus presentation. Contrary to our hypothesis, overall, males and all females did not differ in their level of cue-induced craving; however, when females were separated into groups by cycle phase, FFemales reported significantly less craving than either males or LFemales ($p < .05$). The suppressed craving response in FFemales suggests an influence of cycle phase on cue-induced craving.

Introduction

Crack cocaine smoking, intravenous heroin use, and cigarette smoking are reinforced by the actions of these drugs on mesolimbic dopaminergic brain substrates and by contextual cues associated with the use of each (Breiter & Rosen, 1999; Childress et al., 1999; Foltin & Haney, 2000; Perkins, 1999b; Sell et al., 2000). However, recent studies in cigarette smokers suggest that contextual cues may play a larger role in dependence on cigarettes in females than males. For

example, women respond better to cigarette cessation treatment using putative anticraving medications such as clonidine or mecamylamine, whereas treatment outcomes for men are generally better with nicotine replacement therapy (NRT; Perkins, Donny & Caggiula, 1999). Additionally, pretreatment with nicotine nasal spray reduced smoking to a greater extent in men than in women (Perkins et al., 1992). Women also are less accurate than men at discriminating variations in the amount of nicotine contained in cigarettes or spray (Perkins 1999a; Perkins et al., 1999).

During nicotine cue exposure (an affectively valenced standardized script depicting situations associated with relapse), women reported higher subjective craving than men and displayed greater changes in mean arterial pressure (Niaura et al., 1998). Perkins et al. (2001) have shown that blocking olfactory and taste stimuli associated with smoking reduced subjective ratings of satisfaction in both sexes

Teresa R. Franklin, Ph.D., Kimberly Napier, B.A., Ronald Ehrman, Ph.D., Peter Gariti, Ph.D., Charles P. O'Brien, M.D., Ph.D., and Anna Rose Childress, Ph.D., Addiction Treatment Research Center, Department of Psychiatry, University of Pennsylvania and Veteran's Administration Hospital of Philadelphia.

Correspondence: Teresa R. Franklin, Ph.D., Addiction Treatment Research Center, Department of Psychiatry, University of Pennsylvania, 3900 Chestnut Street, Philadelphia, PA 19104-6178, USA. Tel: +1 (215)-222-3200 x 119; Fax: +1 (215)-386-6770; E-mail: franklin_t@mail.trc.upenn.edu

but decreased ad lib smoking only in females. Work in our own laboratory with cocaine-dependent patients indicated that females were more likely than males to report increased craving in response to cues (Robbins, Ehrman, Childress, & O'Brien, 1999). Overall, these studies may suggest that, in females, smoking-related cues may be more influential in relapse to, or maintenance of, smoking behavior.

Sex differences in smoking indices may be related to hormonal fluctuations that occur throughout the menstrual cycle. Sex hormones have significant effects on the dopaminergic system (Di Paolo, Falardeau, & Morissette, 1988; Morissette, Garcia-Segura, Belanger, & Di Paolo, 1992) implicated in mediating the rewarding and reinforcing effects of nicotine (Di Chiara, 1992). Although few studies have been conducted and the results reported are inconsistent, relationships between menstrual cycle phase and drug-dependent behaviors have been shown. Three studies observed greater postcessation nicotine withdrawal effects in women during the luteal (premenstrual) phase than in women during the follicular (pre-ovulatory) phase of the cycle (Allen, Hatsukami, Christianson, & Brown, 2000; O'Hara, Portser, & Anderson, 1989; Perkins et al., 2000). Further, Allen, Hatsukami, Christianson, and Nelson (1999) observed significantly higher cigarette craving and a stronger desire to relieve negative affect during short-term smoking abstinence in women in the late luteal phase compared with when they were in the follicular phase of their cycle.

To develop effective smoking interventions, it is important to determine the relative contribution to smoking reinforcement of nicotine and stimuli associated with the use of nicotine, and to identify the specific factors related to sex differences observed in addictive behaviors. To determine the influence of menstrual cycle phase on self-report measures of craving, intent to smoke, high, and withdrawal in subjects exposed to smoking stimuli (videos), we retrospectively analyzed these responses in males and in females either in the follicular or luteal phase of their menstrual cycle.

Method

Subjects

Subjects were 109 treatment-seeking individuals taking part in a smoking cessation study involving NRT and different levels of intensity of behavioral treatment. Pre- and post-treatment cue reactivity sessions were run to determine the effects of treatment on cue reactivity. The results of the NRT smoking cessation study have been reported elsewhere (Gariti, Alterman, Mulvaney, & Epperson, 2000). The present report focuses only on self-report data collected during the pretreatment cue reactivity session.

Primary exclusion criteria included medical or other conditions (pregnancy) contraindicating treatment with transdermal nicotine; psychosis or other current severe mental disorders; cognitive dysfunction; non-nicotine psychoactive drug or alcohol abuse during the previous 6-month period; or a positive drug screen at baseline. Psychiatric and drug dependence measures were assessed using the Structured Clinical Interview for DSM-IV (Williams et al., 1992) and the Addiction Severity Index (McLellan, Luborsky, Woody, & O'Brien, 1980). Pregnancy status was confirmed by human chorionic gonadotropin beta blood testing. Written consent was obtained from each participant prior to initiation of study procedures.

The pretreatment cue reactivity session preceded the primary NRT study and did not mandate abstinence. Additional inclusion and exclusion criteria were imposed on NRT study participants to study sex and menstrual cycle effects on cue reactivity. Only subjects aged 18–47 years were included to minimize the possibility of including women in the early stages of menopause. Only nonpregnant premenopausal females who were not on birth control pills, had an average cycle length of 26–30 days, and were without current menstrual difficulties were included. Subjects meeting the primary treatment criteria and the subsequently imposed study-specific criteria were on average 35.6 years of age ($SD=9.7$), smoked on average 26.4 cigarettes per day ($SD=9.7$), and smoked for an average of 18.1 years ($SD=8.1$). Subjects had an average of 15.2 years of education ($SD=3.1$); and 72% were White, 22% Black, 4% Asian, 1% Hispanic, and 1% Other.

Procedures

To reduce craving resulting from pharmacological withdrawal, subjects smoked a cigarette approximately 10 min prior to the cue session. Subjects provided a urine sample for subsequent illicit drug screening and were given a brief oral description of the session.

Prior to and immediately following the cue reactivity session, subjects were administered the Drug Related States Questionnaire (DRSQ; Droungas, Ehrman, Childress, & O'Brien, 1995). This oral questionnaire was modified for use with nicotine-dependent subjects from the Within Session Rating Scale used for other drug dependencies (Ehrman, Robbins, Childress, McLellan, & O'Brien, 1992). The DRSQ gathers subjects' current self-ratings of nicotine-related states. Specifically, subjects are asked to rate on a scale of 1 to 10 (0=not at all and 10=very much) (a) whether they desire a cigarette (craving), (b) whether they would smoke a cigarette if they had the chance (intention to smoke), (c) whether

they feel as if they just had a cigarette (high), and (d) whether they feel edgy, as if they had not had a cigarette in a while (withdrawal).

The cue session consisted of a 15-min video depicting a 30-something heterosexual White American male on a day he is scheduled for a job interview. This video has been validated in our laboratory and contains explicit smoking triggers that induce craving in smoking subjects (Brody et al., 2002; Droungas et al., 1995). In these prior studies, watching a neutral video did not induce craving. The video begins with the male having breakfast with his wife and ends with the procurement of the job. Occasions to smoke, smoking, cigarettes, and other smoking cues are presented throughout the video. The video was shown on a 19-inch color television screen in a sound-attenuated room while subjects sat comfortably in chairs approximately 3–4 feet in front of the screen.

Menstrual cycle phase data was collected from the medical charts and was determined by counting forward from the first day of the last self-reported menstrual flow prior to the session. Days 1–13 were designated the follicular phase (preovulation), and days 15–30 were designated the luteal phase (premenstrual; Perkins et al., 2000).

Results

No significant differences were found in age, number of cigarettes smoked per day, number of years smoking, education, or race among males, FFemales, and LFemales. Prevideo subjective reports for all four measures approached 0 and were not different among males, FFemales, and LFemales, indicating that all groups responded equivalently at baseline. Change scores for craving, intention to smoke, high, or withdrawal were calculated by subtracting the prevideo subjective report scores (baseline) from the postvideo scores. Two analyses were conducted. The

first was a comparison of change scores between males and all females (males, $n=68$; females, $n=41$). Contrary to our primary hypothesis, change scores were not different between males and all females for any of the four subjective measures. In the second analysis, females were separated by cycle phase (males, $n=68$; FFemales, $n=17$; LFemales, $n=24$), and differences among groups were observed (ANOVA; Figure 1). FFemales experienced lower cue-induced nicotine craving than LFemales or males, $F(2, 109)=3.35$, $p<.05$. The Tukey-HSD test with significance set at .05 revealed that craving was significantly suppressed in FFemales (mean=.06, $SD=2.41$, $t=.05$) compared with LFemales (mean=1.92, $SD=1.91$, $t=4.83$) or males (mean=1.41, $SD=2.43$, $t=4.70$). Change scores for self-reported intention to smoke, high, or withdrawal were close to 0 for all groups.

Discussion

We posited an enhanced craving response to smoking cues in females relative to males, and that this response might be influenced by menstrual cycle phase. Our rationale was based on our own cue reactivity data in cocaine-dependent subjects (Robbins et al., 1999); on recent data indicating that males and females respond differently in studies examining smoking-related indices (Niaura et al., 1998; Perkins, 1999a; Perkins et al., 1992, 1999, 2001); and on studies indicating that symptoms such as irritability, difficulty focusing, and anxiety are increased during the luteal phase of the cycle (Van Keep & Leher, 1981) and may influence craving responses. Although craving in response to our smoking cues was not different between males and females before they were separated by cycle phase, it was markedly depressed in FFemales compared either to males or to LFemales. This finding is consistent with the study by Allen et al. (1999)

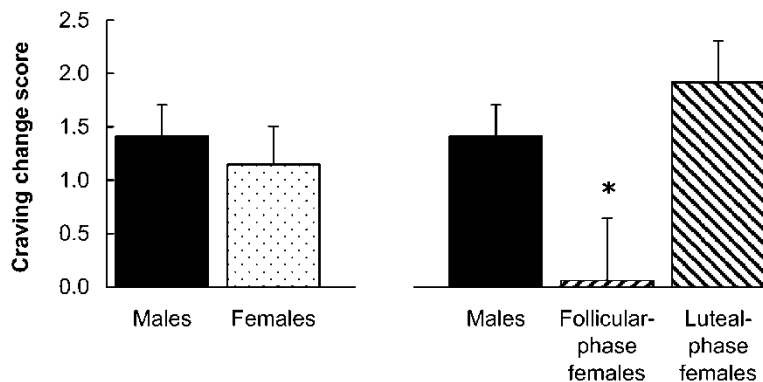


Figure 1. Bars represent postcue minus precue reactivity session craving scores (based on the question “On a scale of 1 to 10, how much do you desire a cigarette at this moment?”) in males, all females (All F), and females in the follicular phase (FF) or in the luteal phase (LF) of the menstrual cycle. Change scores were not different between males and all females (*left*). Females in the follicular phase had significantly lower change scores than females in the luteal phase or males ($p<.05$; *right*).

reporting lower overall craving in smoking women during the follicular phase of their cycle. Because the Allen study did not include males, it was not evident whether craving was diminished in women during the follicular phase or increased in women during the luteal phase. The present data suggest that FFemales experience less craving in relation to LFemales or males.

To our knowledge, this is the first time that data measuring real-time cue reactivity to smoking-related stimuli have been examined with respect to sex and cycle phase. These data demonstrate a difference in cue reactivity in subgroups of females that is masked when all females are grouped together. Cue reactivity differences between males and all females might have been revealed with more power. These data are timely and intriguing because, although published data on the relationships between other smoking behaviors and sex exist, the data are minimal, and even less has been published on the effects of cycle on smoking behaviors. Also, because of contradictory early findings, the issue of sex differences is controversial. For example, sex differences were observed in latency to smoke following cue manipulation (Perkins et al., 2001), amount smoked following exposure to cues (Perkins et al., 1996), and effect of nicotine pretreatment on subsequent smoking (Perkins et al., 1992). However, other studies looking at treatment outcome (Whitlock, Vogt, Hollis, & Lichtenstein, 1997) and withdrawal symptomology (Pomerleau, 1996; Svikis et al., 1986) during quit attempts show no effect of sex. The possibility that the effect of sex on behavior has been confounded by cycle phase biases cannot be ruled out. In fact, animal research is conducted primarily in males because cycle effects contaminate the data to such an extent that they are not interpretable. An examination of the differences between male and female neuro-correlates and behavior in the animal literature should convince us that studying such effects in humans is crucial to our complete understanding of dependence (Campbell, Morgan, & Carroll, 2002; Donny et al., 2000; Koyle, Demircoren, London, & Pogun, 1997).

Change scores hovered near 0 for self-reported withdrawal, high, and intent to smoke in all three groups and were not different among groups. Withdrawal change scores were not expected to differ pre- and postvideo because subjects had smoked a cigarette immediately before the session. The temporal proximity of cigarette smoking to the cue reactivity session may have reduced high and intent to smoke responses as well. Alternatively, a larger number of subjects or a more precise method of assessing cycle phase may be necessary to reveal differences in change scores for withdrawal, high, and intent to smoke. The fact that baseline and change scores for withdrawal, high, and intent to smoke were not different between FFemales

and LFemales suggests that the difference in craving change scores was not related to increasing negative mood, irritability, or impaired concentration, often associated with the luteal phase (Allen et al., 1999). Thus, the urge to smoke was selectively decreased in FFemales and did not appear to be a consequence of response bias in self-report associated with cycle phase.

One plausible explanation for the phase-related differences observed in cue-induced craving responses may be related to hormonal influences. The concentrations and ratios of circulating sex hormones oscillate throughout the menstrual cycle: Estrogen levels rise during the follicular phase, whereas progesterone levels are low during the follicular phase and peak in midluteal phase. Preclinical studies show that elements of the dopaminergic system (*i.e.*, receptors, transporters, and dopamine itself) strongly implicated in mediating conditioned responses fluctuate coincident with peak plasma estradiol and progesterone concentrations (Morissette & Di Paolo, 1993; Morissette et al., 1992), although not all studies show the same correlations between hormone levels and components of the dopaminergic system (Nordstrom, Olsson, & Halldin, 1998). Hormone levels were not measured in this retrospective study. Nevertheless, it is tempting to speculate that the composition of circulating sex hormones during the follicular phase of the cycle may exert a protective effect on cue-induced craving.

These data are valuable to our early understanding of the contribution of cycle phase to cigarette craving, yet they are limited because of the absence of hormone concentration measures and a more precise assessment of cycle phase. Cycle phase was based on subject self-report of menstrual cycle length and the first day of the last menstrual flow. Information pertaining to subsequent menses, which would be helpful in determining cycle phase more definitively, was not available. However, generally, females are aware of particular features of their cycle and are regularly asked questions about it during routine physical examinations, because a normal cycle is indicative of good health. The fact that a significant difference in craving to cues was shown using a nonphysiological measure of cycle phase suggests a robust effect and provides useful and relevant data to aid in formulating and testing hypotheses. Nevertheless, these results point to the necessity of including definitive measures of cycle phase in future studies of smoking-related and possibly other drug-related behaviors. These preliminary results show that treatment-seeking LFemales are more responsive to cues than FFemales and demand our attention, because cycle phase may play a role in relapse.

Continued investigations into the role of the menstrual cycle in smoking-related behaviors are necessary and may reveal similar cycle-related

behavioral distinctions. Cycle phase influences likely may generalize to other abused substances, and valuable treatment aids may result from including cycle phase assessments in studies of pathological drug and alcohol use. Further, these data support a growing dataset indicating that males and females should be studied independently and that menstrual cycle phase may be important to our understanding of the differences between sexes.

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