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Effect of menstrual cycle on ethanol drinking in rhesus monkeys

Sydney G. Thomas, Paul W. Czoty*

Department of Physiology & Pharmacology, Wake Forest School of Medicine, Winston-Salem, NC 27157, United States

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ABSTRACT

Background: Sex differences in the abuse-related effects of alcohol have been demonstrated in the clinic and in preclinical animal models. Less is known about the influence of menstrual cycle phase on drinking.

Methods: In this study, we examined the relationship between menstrual cycle phase and intake of ethanol (EtOH) in five adult female rhesus monkeys. Subjects consumed a 4% EtOH solution in their home cage 6 h per day, 5 days per week and pressed a lever to receive food pellets during the drinking session. Menstrual cycle was determined with vaginal swabs 5–7 days per week. To facilitate comparison with previous studies, the cycle was divided three different ways for analysis.

Results: First, no significant difference was observed when EtOH intake was compared between phases defined as "follicular" (days 5–10) and "luteal" (19–24). Second, when the cycle was further divided into four phases [early follicular (days 1–7), late follicular (8–14), early luteal (15–21) and late luteal (22-next cycle)], significant differences were detected, with intake highest in phases that bracket menses and lowest in the late follicular phase. Finally, EtOH intake during "mid-cycle" (days 12–16) was significantly lower than during "menses" (days 1–5) and "late luteal" (last 5 days). Effect sizes were small to moderate, although absolute differences in EtOH intake (g/kg) were < 15%. Food-maintained responding was not different across phases.

Conclusions: Menstrual cycle has modest but statistically significant and selective effects on EtOH drinking, with higher EtOH intake observed in the peri-menstrual period compared to the middle of the cycle.

1. Introduction

Excessive alcohol drinking and alcohol use disorder (AUD) persist as major public health problems, resulting in ~80,000 deaths and costing > $223 billion per year in the US alone (Kanny et al., 2013). The development of effective medications requires an understanding of the how characteristics of individual patients affects their response to medication. For example, sex differences in the effects of alcohol are well-documented (see Becker and Koob, 2016); understanding how both alcohol and putative medications differentially affect men and women will permit development of sex-specific pharmacotherapies. Less is known about the interaction of menstrual cycle phase with the abuse-related effects of alcohol. Considering that interactions between drugs and gonadal hormones likely underlie male-female differences, it is of further interest to determine whether hormonal fluctuations across the menstrual cycle alter the effects of alcohol.

The question of whether drinking differs across the menstrual cycle has long been of interest. Early clinical studies, primarily consisting of retrospective reports and reviews of medical charts, supported the hypothesis that women increase alcohol intake just prior to or during menses to relieve associated dysphoria (e.g. Belfer et al., 1971; Podolsky, 1963). These studies had several limitations (reviewed in Tate and Charett, 1991), and early prospective reports found an opposite or no association between menstrual cycle phase and alcohol drinking (e.g., Griffin et al., 1987; Harvey and Beckman, 1985; Jones and Jones, 1984; Mello et al., 1986; Sutker et al., 1983). Other studies found no correlation between symptom severity and alcohol intake (e.g., Tate and Charette, 1991; Tate and Charette, 1991). Several reviews have identified methodological differences that likely underlie the discrepant results observed in human studies over the past six decades (e.g., Carroll et al., 2015; Gill, 1997; Lammers et al., 1995; Tate and Charette, 1991).

Studies in animal models lack some of the confounds inherent in human studies and allow for greater experimental and environmental control. Nonhuman primates have particular advantages that make them ideal research subjects in models of AUD (Grant and Bennett, 2003; Phillips et al., 2014; Weerts et al., 2007). Although important knowledge can be gained about the neuropharmacology of ethanol (EtOH) in rodents, the ability to generate clinically relevant phenotypes related to long-term drinking is limited in rodent species. Regarding

* Corresponding author at: Department of Physiology and Pharmacology, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1083, United States.
E-mail address: pczoty@wakehealth.edu (P.W. Czoty).

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studies of the interaction between menstrual cycle and alcohol drinking, nonhuman primate models are particularly valuable. Unlike rodents, which have a 4-day estrous cycle, the menstrual cycle of macaques (which include cynomolgus and rhesus monkeys) is similar to humans, with a duration of approximately 28 days and well-characterized fluctuations in estradiol and progesterone (Appt, 2004; Goodman et al., 1977; Jewitt and Dukelow, 1972). Only one study in nonhuman primates has directly assessed whether alcohol self-administration differs across the menstrual cycle (Mello et al., 1986). Female rhesus monkeys were trained to press a lever to receive intravenous (i.v.) injections of EtOH (0.12 g/kg per injection). Although monkeys who self-administered less than 1.5 g/kg per day tended to consume less in the middle of the cycle compared to the peri-menstrual period, different relationships between phase and intake were observed in the majority of monkeys who consumed more than 1.5 g/kg per day. Other relevant data include studies that used a drug discrimination procedure, which models the subjective effects of drugs. Grant and colleagues trained cynomolgus monkeys to discriminate orally administered EtOH (1 or 2 g/kg) from water (Grant et al., 1997; Green et al., 1999). Monkeys were more sensitive to the discriminative stimulus effects of EtOH during the luteal phase (around day 17 of cycle), but that effect diminished when the higher training dose was used.

In the present report, we examined data from five adult female rhesus monkeys to determine whether EtOH intake differed across the menstrual cycle. One noted confound in previous studies was variation in or absence of definition of specific menstrual cycle phases and inconsistencies as to which portions of the cycle were compared (e.g., Carroll et al., 2015). Thus, we analyzed data in three ways. First, we assessed whether drinking differed between "follicular" and "luteal" phases, defined as days 5–10 and 19–24 of the cycle, respectively. Next, we further divided the cycle into four divisions: early follicular (days 1–7), late follicular (days 8–14), early luteal (days 15–21) and late luteal (days 22-onset of next cycle) to better match the changing milieu of ovarian hormones. Finally, we compared drinking at three points of the cycle, similar to Mello et al. (1986). We compared the first 5 days of the cycle ("menstruation"), 5 days in the middle of the cycle ("mid-cycle," days 12–16) and the last 5 days of the cycle ("late luteal" phase).

2. Materials and methods

2.1. Subjects

Five adult female rhesus monkeys (*Macaca mulatta*), with an average (± SD) age of 8.7 (± 1.0) years, were housed individually in 0.83 × 0.71 × 0.78 m stainless steel cages (0.76 × 0.83 × 0.83 m) in a vivarium maintained at 24 °C and ~25–30% humidity with a 12:12 light/dark cycle. All monkeys had been trained to drink a solution of 4% ethanol in water using schedule induction (Vivian et al., 2001). At the outset of these studies, monkeys had been consuming EtOH 5 days per week for approximately 1.5 years with a mean (± SD) lifetime EtOH intake of 815.5 ± 81.6 g/kg (Table 1). Monkeys were fed in the form of 1-g, banana-flavored pellets (Bio-Serv, Flemington, NJ) delivered during the behavioral session (see below), supplemented with fruit/vegetables. Monkeys were fed enough food daily to maintain healthy weights as determined by daily visual inspection and periodic veterinary examinations. All procedures were approved by the Wake Forest University Animal Care and Use Committee and were performed in accordance with the 2011 National Research Council *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research*. Environmental enrichment was provided as outlined in the Animal Care and Use Committee of Wake Forest University Non-Human Primate Environmental Enrichment Plan.

2.2. Apparatus

Access to food pellets and ethanol was controlled via an operant ("drinking") panel attached to one wall of the cage described previously (Vivian et al., 2001). Drinking panels contained two drinking spouts, a set of three 2.8-W lights (red, amber, and green) above each spout, a retractable lever below one of the spouts and a 2.8-W white light and dowel within a centrally positioned opening. An active panel was signaled by illumination of amber lights; correct placement of the hand and pulling of the dowel was signaled by illumination of white and green lights. Illumination of the green lights indicated that fluid and food were available. Red lights signaled a fluid flow of approximately 1.5 ml/sec. Each drinking panel was connected to an individual EtOH reservoir (2-L bottle), positioned atop a balance that continuously monitored weight displacement which was subsequently converted to volume displacement. Correct placement of the hand and pulling the dowel operated solenoid valves that allowed EtOH to become available. Fluid flow via gravity was accomplished when the EtOH spout was displaced approximately 2 mm in any direction, and greater volumes were delivered when negative pressure was also applied. When the monkey failed to displace the spout or removed her hand from the dowel, fluid flow stopped. Thus, volumes and rates of EtOH consumed were determined solely by the monkey. Ethanol (95% ethyl alcohol) was obtained from The Warner-Graham Company (Cockeysville, MD) and diluted each morning in water purified by reverse osmosis.

2.3. Induction and maintenance of EtOH self-administration

All monkeys had previously been trained to use the drinking panel through a method of hand-shaping. Once monkeys reliably pressed the lever to deliver a food pellet and pulled the dowel to operate the drinking spout (and reliably drank water from the spout), induction commenced (in July 2014). Under this procedure, food pellets were delivered every 300 s with the lever retracted; this schedule of pellet delivery induces polydipsia. For the first 3 weeks, water was available from the spout. Daily sessions began at 11:00 am and lasted until 250 ml of water were consumed. After 3 weeks, the drinking solution was changed to 4% EtOH (w/v, made fresh each day) and sessions ended once the monkey consumed 0.5 g/kg EtOH. For the next 4 weeks, sessions were identical except that they ended once 1.0 g/kg was consumed. For the last 4 weeks of induction, sessions ended when monkeys consumed 1.5 g/kg. Following this 15-week regimen, scheduled pellet deliveries were discontinued and 4% EtOH was available 22 h per day, 5 days per week. On the other 2 days of the week, panels were inoperative.

Table 1
Ethanol intake history (in g/kg) and menstrual cycle parameters for each subject.

	Ethanol Intake (g/kg)			Menstrual Cycles		
	End of induction	Start of study	End of study	Cycles used	Mean length (days)	Cycles omitted
C-1542	126.7	937.0	2794.5	29	28.6 ± 4.0	3
C-1243	130.9	640.3	1861.2	27	28.1 ± 1.8	4
C-1544	131.2	747.5	2736.7	22	32.0 ± 4.6	5
C-1324	126.9	1032.8	2769.1	28	27.6 ± 2.1	3
C-1680	131.1	719.7	2142.6	28	27.0 ± 2.0	3

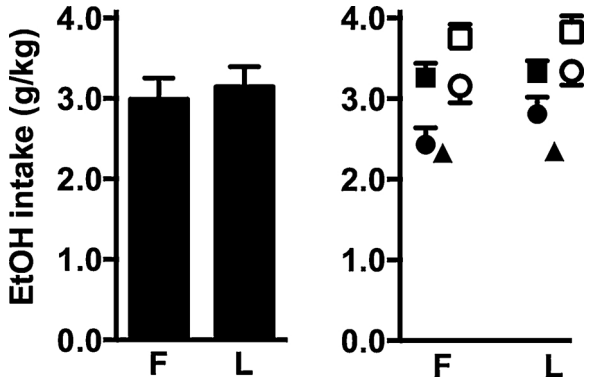

Fig. 1. EtOH intake: Follicular vs. Luteal phases. Mean (± SEM) EtOH consumption (g/kg) during follicular phase (F, days 5–10) and luteal phase (L, days 19–24) of the menstrual cycle. Left, group data. Right, data from individual subjects, represented by different symbols.

On days of EtOH drinking sessions, food was available in 3 "meals." In each meal, monkeys earned 1/3 of their daily food allotment by responding on the lever for food pellets (Bio-serv; Flemington, NJ). The first meal started at the beginning of the drinking session (11:00 am); other meals began 2 and 4 h later. On days on which monkeys did not partake in an EtOH drinking session, the day's entire pellet allotment was administered at approximately 11:00 a.m. Drinking sessions lasted 22 h. Each day at 9:00 am (when the previous day's session ended), technical staff entered the room, refilled the feeders and fluid reservoirs, downloaded data and restarted the session at 11:00 am. In October 2015, after 8.5 months of drinking under the 22-hr condition, conditions were changed such that drinking sessions lasted only 6 h. This change was made to optimize experimental conditions for a study examining the effect of opioidergic drugs that was initiated shortly thereafter (Flynn et al., unpublished data). One month later, once average daily EtOH intakes had stabilized, the current study began.

2.4. Menstrual cycle assessment

Menstrual cycles were monitored beginning one month after the onset of the 6-hr drinking sessions (i.e., November 2015). Just prior to the start of each drinking session, vaginal swabs were performed on each monkey, and the presence or absence of blood was noted; the first observation of blood indicated menses and Day 1 of a cycle. Later in the experiment, swabbing was performed on some weekends as well.

2.5. Data analysis

Data were collected over 32 months, from November 2015 to June 2018. The primary dependent variables were the amount of ethanol consumed (in g/kg) and number of food pellets delivered. Phases were defined in three ways for analysis. In the first analysis, cycle phases were defined as "follicular" (days 5–10) and "luteal" (19–24). Data from these phases were compared using a paired t-test. In the second analysis, four divisions of the cycle were compared, defined as early follicular (days 1–7), late follicular (8–14), early "luteal" (15–21), and "late luteal" (22-next onset), using a repeated-measures one-way analysis of variance (ANOVA), followed by post-hoc testing using Tukey's multiple comparisons test. The third method of analysis, three 5-day sections of the cycle were compared ["menstruation" (days 1–5), "mid-cycle" (days 12–16) and the last 5 days of the cycle ("late luteal" phase)] using a repeated-measures one-way ANOVA and Tukey's multiple comparisons test. Where differences were observed, Cohen's *d* was calculated to determine effect size. Differences were considered significant at the 95% level of confidence ($p < 0.05$).

3. Results

3.1. Characteristics of menstrual cycles

All monkeys cycled normally throughout the current study. Some cycles were omitted from analysis for two reasons (Table 1). First, during a portion of this time, monkeys served as subjects in studies of the effects of drugs that interact with mu opioid receptors and nociceptin/orphanin FQ receptors (Flynn and Czoty, unpublished results). Cycles in which such drug testing took place were not included in the present analyses (2–5 per monkey); self-administration data were also omitted from analysis in the present study. In addition, for one monkey, two cycles were omitted because menses could not be verified. Despite these omissions, the average number of cycles analyzed was 26.8 ± 1.4 (Table 1). Day 1 of the cycle was not more or less likely to occur on any specific day of the week.

3.2. Effects of menstrual cycle phase on behavior

When the "follicular" (days 5–10) and "luteal" (days 19–24) phases were compared (Fig. 1), there was no significant difference in EtOH intake or food pellets delivered (not shown). When the cycle was divided into four parts (Fig. 2), a one-way repeated-measures ANOVA revealed a main effect of phase ($F_{3,12} = 13.27$, $p < 0.01$) on EtOH intake. Post-hoc testing indicated significant differences between the amount of EtOH consumed in the early vs. late follicular phase, early vs. late luteal phase and late follicular vs. late luteal. Effect sizes were determined to be small for the difference between early and late follicular phases (Cohen's $d = 0.323$) and between the early and late luteal phases (0.256); effect size was moderate for the difference between the late follicular and late luteal phases (0.505). There were no significant differences in food pellets delivered across the four phases (not shown). Finally, when 5-day sections of the cycle were compared as in Mello

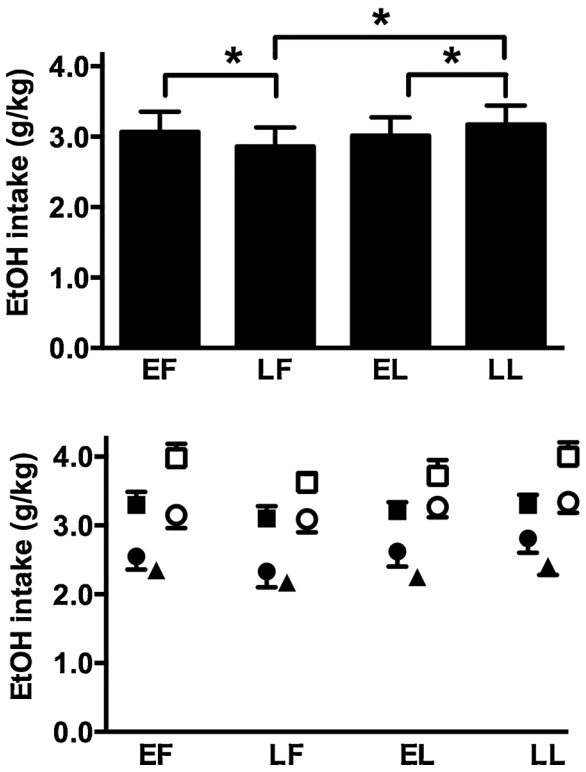

Fig. 2. EtOH intake: Early and late follicular and luteal phases. Mean (± SEM) EtOH consumption (g/kg) during four phases of the menstrual cycle: EF (days 1–7), LF (days 8–14), EL (days 15–21) and LL (days 22-onset of next cycle)*, $p < 0.05$. Otherwise as in Fig. 1.

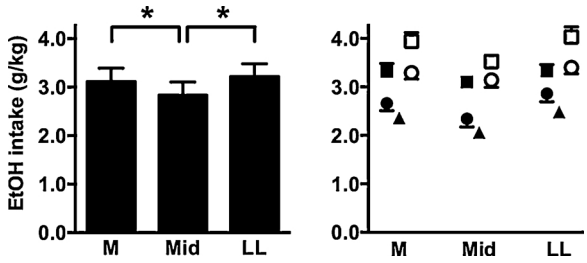

Fig. 3. EtOH intake: Menstruation vs. mid-cycle vs. luteal phases. Mean (± SEM) EtOH consumption (g/kg) during three segments of the menstrual cycle: menstruation (days 1–5), mid-cycle (Mid, days 12–16) and LL (last 5 days). Otherwise as in Fig. 1.

et al. (1986), a one-way repeated-measures ANOVA revealed a main effect of phase ($F_{2,8} = 35.67$, $p < 0.01$; Fig. 3). Post-hoc multiple comparisons testing revealed that EtOH intake during mid-cycle (days 12–16) differed significantly from intake during menstruation (days 1–5) and during late luteal phase (last 5 days of the cycle). Effect sizes were moderate (Cohen's $d = 0.460$ and 0.6494, respectively). There were no significant differences in food pellets delivered (not shown).

4. Discussion

Males and females differ in vulnerability to develop substance use disorders, in the trajectory of such disorders and in response to treatment. It is likely that these sex differences are mediated at least in part by ovarian hormones. Thus it is reasonable to hypothesize that fluctuations in ovarian hormones across the menstrual cycle may modulate the abuse-related effects of drugs in females. Results of early clinical studies supported the hypothesis that women increase alcohol intake during the peri-menstrual period (e.g. Belfer et al., 1971; Podolsky, 1963). However, this conclusion has not been consistently supported (e.g. Charette et al., 1990). As described above, these discrepancies may be due to variations in experimental design and other limitations inherent to human subjects research (e.g. retrospective reports).

The present study addressed this question using a well-characterized, highly translational nonhuman primate model of EtOH consumption (Baker et al., 2014; Vivian et al., 2001). Adult female rhesus monkeys with extensive experience drinking EtOH had free access to EtOH 6 h per day, 5 days per week. Importantly, despite consistently consuming ≥ 2.8 g/kg EtOH per day, monkeys cycled normally throughout the time of the study; average cycle duration across monkeys was 28.7 ± 1.0 days. To facilitate comparison of our data with previous and future studies, we analyzed drinking data in three ways. First, the most simplistic division of the menstrual cycle defines two phases. Follicular phase begins the first day of menses and ends at ovulation, approximately day 14. The remainder of the cycle is considered the luteal phase. When a 6-day section in the middle of these two phases was compared, no significant differences were observed in EtOH intake or in the number of food pellets delivered. These data support the hypothesis that cycle does not affect drinking, but leaves open the possibility that fluctuations may occur that are not captured by simply comparing mid-follicular and mid-luteal time points.

To address the latter possibility, we then divided the cycle into four sections rather than two. These divisions were made to reflect changing levels of progesterone and estradiol across the cycle (e.g. Appt et al., 2009; Kromrey et al., 2015). During the EF phase both hormones are relatively low. Estradiol increases and peaks during the LF phase. During the EL phase estradiol declines and progesterone peaks. Progesterone then declines during the LF phase. This analysis revealed differences in EtOH intake across the cycle that were statistically significant. Specifically, monkeys drank less EtOH in the peri-ovulatory phases (LF and EL) than in the peri-menstrual phases (LL and EF). These data are consistent with an inhibitory role of estradiol on EtOH intake as has been observed in rodents (Ford et al., 2002). A limitation of the present study, however, is that concentrations of ovarian hormones were not collected. Future studies that monitor serum levels of these hormones would more directly link fluctuations in ovarian hormones with changes in EtOH intake and could implicate specific ovarian hormones directly.

As a final method of analysis, we considered early clinical studies of the relationship between menstrual cycle and alcohol intake. Rather than highlighting follicular/luteal differences, these investigators focused on the peri-menstrual period as a time that women may increase their drinking to cope with mood changes and/or physical discomfort (e.g. Belfer et al., 1971; Podolsky, 1963). The only nonhuman primate study to examine alcohol self-administration across the menstrual cycle used this approach (Mello et al., 1986). Female rhesus monkeys self-administered i.v. injections of EtOH. Data were analyzed across three 5-day phases of the menstrual cycle: menses (days 1–5), mid-cycle (days 12–16) and late luteal (last 5 days). To directly compare the present data with those of Mello et al., our data were analyzed similarly.

Two important considerations in comparing the present data with those of Mello et al. (1986) are the route of administration and overall EtOH intake. In the Mello et al. (1986) study, differences in EtOH intake between phases were observed, but the relationships were qualitatively different depending on monkeys' EtOH intake. In monkeys that self-administered 0–1.5 g/kg per day, intake was significantly lower in mid-cycle versus menses or late luteal. In monkeys that self-administered 1.5–3.0 g/kg per day, there were no differences across phases. Different relationships were observed in monkeys with daily intakes greater than 3.0 g/kg per day. Mello et al. (1986) used i.v. EtOH which, unlike the oral EtOH method used in the present study, does not undergo first-pass metabolism. Thus, monkeys in the present study, who drank approximately 2.5–3.3 g/kg per day might be most comparable with the low-intake monkeys of the Mello et al (1986) study. Indeed, when the present data were analyzed in the manner of Mello et al. (1986), EtOH intakes during the mid-cycle block of days was significantly lower than both menstruation and late luteal phases. Results indicate that data obtained with i.v. EtOH self-administration techniques are more likely to recapitulate data collected under more translational oral self-administration methods when levels of i.v. self- administration are low. They also suggest that different relationships between cycle phase and EtOH intake may have been obtained in the present study if EtOH intakes were higher. However, it is important to note that in the present study, total EtOH intake was entirely under the control of the subjects themselves.

Taken together, data from the two nonhuman primate studies are in agreement with early clinical conclusions that drinking is generally higher around the time of menses. The lack of effect of phase on food-maintained responding suggests that the observed reductions in drinking were specific to EtOH and not due to sedation, motor impairment, or a general unwillingness to engage in the task. Although the absolute decline in EtOH intake was less than 15%, effect sizes were small to moderate. Thus it will be important that future studies be designed to control for fluctuations in drinking across the cycle. For example, it is possible that susceptibility of drinking to pharmacological or environmental modulation could show greater sensitivity to cycle phase than was observed here. Moreover, the present results suggest that a simple follicular/luteal split is not sufficient to capture this dynamic process. Analysis strategies should capture the increase in drinking that occurs in the peri-menstrual period, and the trough that occurs near the middle of the cycle.

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Contributors

Thomas and Czoty participated in the research design, conducted experiments, performed data analysis and wrote the manuscript.

Conflict of interest

No conflict declared.

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