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Response to alcohol in women: Role of the menstrual cycle and a family history of alcoholism

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ABSTRACT

The present study determined whether: (1) the response to alcohol varied as a function of menstrual cycle phase and (2) women with a paternal history of alcoholism (FHP) were less sensitive to the effects of alcohol compared to women without a family history of alcoholism (FHN). The behavioral effects of alcohol (0.00, 0.25, and 0.75 g/kg) were evaluated in 21 FHN and 24 FHP women; each dose was tested during both the midfollicular and late luteal phases of the menstrual cycle. Baseline negative mood was increased during the luteal phase compared to the follicular phase (increased Beck Depression scores and decreased Vigor, Arousal, and Friendly scores). Alcohol increased ratings of Drug Liking and Good Drug Effect more in the luteal phase than the follicular phase. FHP women had greater negative mood during the luteal phase and some of these dysphoric effects were increased by alcohol more in FHP women than FHN women. Alcohol impaired performance, with no group or menstrual cycle differences. However, consistent with previous studies, FHP women were less impaired by alcohol than FHN women on the balance task. These data indicate that (1) the differences in response to alcohol across the menstrual cycle are subtle, although alcohol is liked more during the luteal phase; (2) increases in dysphoric mood during the luteal phase are more pronounced in FHP women compared to FHN women, particularly after alcohol; and (3) the differences observed in response to alcohol between FHP and FHN women are less pronounced than previously shown in men.

1. Introduction

Even though women generally consume less alcohol than men (Dawson and Archer, 1992) and have lower rates of alcoholism than men (Kessler et al., 1994), alcohol consumption among women has been increasing, particularly in young women (Mercer and Khavari, 1990; Wilsnack et al., 1994). A recent study confirmed that the gender gap in the U.S. is decreasing with respect to both alcohol consumption and alcohol use disorders (Keyes et al., 2008). Specifically, Keyes et al. (2008) found that among the youngest cohort of women, 16% reported a lifetime prevalence of frequent binge drinking compared to only 2% of the oldest cohort of women. Further, among the youngest cohort, the odds of men binge drinking was 2.66 times higher than for women, whereas in the oldest cohort, men were 10.55 times more likely to binge drink than women. Clearly alcohol consumption is increasing among women. Given that earlier studies showed that women progressed more rapidly to alcoholism (i.e. "telescoping"), despite drinking substantially less alcohol than men (Piazza et al., 1989; Ross, 1989), the rise in alcohol consumption among women is particularly concerning as it will likely further increase the prevalence of alcohol abuse and dependence in women.

Despite the increases in alcohol consumption among women, relatively few studies have adequately evaluated the behavioral effects of alcohol in women and the factors that may influence their response to alcohol under controlled conditions. One factor that may influence alcohol consumption or the behavioral response to alcohol in women is the menstrual cycle. In terms of alcohol pharmacokinetics across the menstrual cycle, the results of initial studies were inconclusive (see reviews by Gill, 1997; Lammers et al., 1995), while more recent studies have consistently failed to observe differences in alcohol pharmacokinetics across the menstrual cycle (Correa and Oga, 2004; Holdstock and de Wit, 2000). Similarly, early studies provided some suggestive evidence that the behavioral effects of alcohol varied across the menstrual cycle, but the findings across studies have been inconsistent and inconclusive in large part due to design limitations such as relying on self-reported drinking,

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not carefully monitoring or verifying menstrual cycle phase with hormone levels of estradiol and progesterone, small sample sizes, or a combination of these factors.

Only a few studies have carefully assessed the role of the menstrual cycle on the behavioral response to alcohol in women under controlled laboratory conditions in which menstrual cycle was confirmed with hormone levels. One study reported a greater reduction in saccadic eye movement in the late luteal phase compared to the midfollicular phase in 12 women with premenstrual dysphoric disorder, but not in 12 control women, following an intravenous infusion of alcohol (Nyberg et al., 2004). However, in that study, ratings of intoxication did not vary as a function of menstrual cycle phase in either group. Mumenthaler et al. (2001) found no differences in flight simulator performance or alcohol pharmacokinetics between the early follicular and midluteal phases of the menstrual cycle following alcohol administration (0.67 g/kg) among 24 female pilots. Lastly, Holdstock and de Wit (2000) tested 16 women at four distinct phases of the menstrual cycle (early follicular, late follicular, midluteal, late luteal) using a cumulative dosing alcohol procedure and the subjective effects, performance effects and alcohol choice did not vary across the menstrual cycle. At this time, there is limited evidence that menstrual cycle phase substantially alters either the pharmacokinetic or behavioral effects of alcohol, but these conclusions are based on a small number of carefully controlled laboratory studies and more definitive studies are needed.

Another factor that has been shown to alter the response to alcohol, particularly in men, is having a family history of alcoholism. In fact, a family history of alcoholism is one of the best predictors of subsequent alcohol abuse or dependence (Hinckers et al., 2006; Warner et al., 2007). A number of studies, primarily by Schuckit and colleagues, have shown that males with a first-degree family history of alcoholism (FHP) are less sensitive (i.e., have a low level of response) to the subjective and performance-impairing effects of alcohol (e.g., Pollock et al., 1986; Schuckit, 1984, 1985). These results were supported by a meta-analysis of 17 independent studies (Pollock, 1992) and a 10-year follow-up study showed that males who were less sensitive to the behavioral effects of alcohol were more likely to develop alcoholism, particularly if they had an alcoholic father (Schuckit, 1994). It should be noted that not all alcohol challenge studies in FHP males have shown a low response compared to FHN males (McCaul et al., 1990, 1991a,b; Newlin and Thompson, 1991, 1999; O'Malley and Maisto, 1985).

In contrast to the abundant number of alcohol challenge studies in FHP men, substantially fewer studies have assessed the behavioral response to alcohol in FHP women, with early studies reporting inconsistent differences between FHP and FHN females (Lex et al., 1988, 1994; Savoie et al., 1988). Over the last decade, studies with larger sample sizes have been conducted in FHP women. For instance, Schuckit et al. (2000) reported that FHP males ($n = 75$) and FHP females ($n = 38$) showed decreased ratings of intoxication and less impairment on body sway following a single dose of alcohol compared to FHN males ($n = 68$). However, that study reported no significant differences between FHP females and FHN females and this was attributed to the small sample of FHN females ($n = 11$). A more recent study compared ratings of intoxication and body sway following a single dose of alcohol in 25 FHP and 25 FHN females (Eng et al., 2005). Despite this larger sample, FHP women only showed significantly lower intoxication ratings at a single time point. Even after drug use, drinking history and breath alcohol levels were used as covariates and body sway data were corrected and transformed for skewness, there were minimal differences between FHP and FHN women on ratings of intoxication or body sway. In a previous study conducted in our laboratory (Evans and Levin, 2003), the role of a paternal history of alcoholism in response to alcohol (0, 0.25, 0.50, and 0.75 g/kg) was assessed in 16 FHP women compared to 16 FHN women. Consistent with previous studies showing that FHP individuals have a lower response to alcohol, FHP women were less impaired by alcohol than FHN women, as shown by scores on the Digit Symbol Substitution Task (DSST) and observer-ratings of drug effect, but FHP women tended to report greater positive subjective effects than FHN women. Thus, at this time, in contrast to men, there is limited compelling evidence that FHP women have a low response to alcohol compared to FHN women.

A potential limitation of the alcohol response studies in FHP women conducted thus far is that the role of the menstrual cycle has been ignored. However, the study by Evans and Levin (2003) observed that FHP women reported more dysphoric mood than FHN women in the absence of drug administration, a finding that has been reported by other studies in FHP individuals (Ciraulo et al., 1996; Evans et al., 2000; Moss et al., 1989; de Wit and McCracken, 1990). At least among the studies involving FHP women (Ciraulo et al., 1996; Evans et al., 2000; Evans and Levin, 2003), these baseline differences in dysphoric mood might be related to dysphoric mood changes that occur in some women during different phases of the menstrual cycle, particularly the late luteal phase and the early follicular phase. To our knowledge, no studies have directly addressed whether the response to alcohol varies in FHP women across the menstrual cycle and studies that did investigate the effects of alcohol across the menstrual cycle either did not measure or did not report whether participants had family histories of alcoholism (e.g., Mumenthaler et al., 2001; Nyberg et al., 2004; but see Holdstock and de Wit, 2000). Thus, it remains unknown whether the response to alcohol varies across the menstrual cycle in FHP women.

Therefore, the present study was designed to improve and extend the previous alcohol challenge studies in women, with three primary objectives. The first objective was to conduct a controlled laboratory study to comprehensively assess the behavioral and subjective response to alcohol at different phases of the menstrual cycle in a large sample of women ($n = 45$). Since there is some evidence that women may drink more during the late luteal phase, we compared the effects of alcohol during the late luteal phase to the midfollicular phase (e.g., Harvey and Beckman, 1985; McLeod et al., 1994; Podolsky, 1963; Mello et al., 1990). The second objective was to extend our previous findings (Evans and Levin, 2003) and those of Eng et al. (2005) on the role of a family history of alcoholism in response to alcohol in women since this sample of 45 women consisted of 24 FHP and 21 FHN women. In the present study, FHP women had a confirmed paternal history of alcoholism (those with a maternal history of alcoholism were excluded) and FHN women had no first-degree family history of alcoholism or substance abuse. Lastly, in light of the baseline dysphoric mood changes observed previously in FHP women compared to FHN women, the third objective was to determine if there were any interactions between family history status and menstrual cycle phase on mood.

2. Materials and methods

2.1. Participants

Women who participated in this study responded to an advertisement in local newspapers recruiting female volunteers with and without a family history of alcoholism. Individuals were told that the purpose of the study was to determine the effects of various drugs (non-prescription or prescription) and alcohol on mood, vital signs and ability to perform certain tasks across the menstrual cycle. The Institutional Review Board of the New York State Psychiatric Institute approved this study. Participants gave their written informed consent before beginning the study and were paid for their participation.