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Sex differences in acute hormonal and subjective response to naltrexone: The impact of menstrual cycle phase

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Summary Women often exhibit larger hormonal and subjective responses to opioid receptor antagonists than men, but the biological mechanisms mediating this effect remain unclear. Among women, fluctuations in estradiol (E2) and progesterone (P4) across the menstrual cycle (MC) affect the endogenous opioid system. Therefore, the goal of the current study was to compare acute naltrexone response between women in the early follicular phase of the MC (low E2 and P4), women in the luteal phase of the MC (high E2 and P4), and men. Seventy healthy controls ($n = 46$ women) participated in two morning sessions in which they received 50 mg naltrexone or placebo in a randomized, counterbalanced order. Women were randomized to complete both sessions in either the early follicular ($n = 23$) or luteal phase of the MC. Serum cortisol, salivary cortisol, prolactin, luteinizing hormone (LH), and subjective response were assessed upon arrival to the laboratory and at regular intervals after pill administration. In luteal and early follicular women but not men, naltrexone (vs. placebo) increased serum cortisol and prolactin levels from baseline; however, the naltrexone-induced increases in these hormones were significantly greater in luteal women than early follicular women. Additionally, only luteal women demonstrated an increase from baseline in salivary cortisol levels and the severity of adverse drug effects in response to naltrexone. In sum, the results indicate that luteal phase women are more sensitive to acute hormonal and subjective effects of naltrexone than early follicular women and men. These findings may have important implications for the use of naltrexone in women.

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1. Introduction

The opioid receptor antagonist naltrexone is an approved pharmacotherapy in the treatment of alcohol and opioid dependence and is currently under investigation for use in other addictive behaviors (Comer et al., 2013; King et al., 2012). Several studies have reported a high degree of individual variability in treatment response to naltrexone, which has been theorized to contribute to naltrexone's modest efficacy in treating alcohol use disorders (Kranzler and Van Kirk, 2001; Ray et al., 2010; Rosner et al., 2010; Streeton and Whelan, 2001). As other opioid receptor antagonists are also effective in the treatment of alcohol use disorders (e.g., nalmefene; Mann et al., 2013) and are commonly used as probes of hormonal function (e.g., naloxone), understanding factors that contribute to individual differences in response to opioid receptor antagonists is a priority. While most studies of individual differences have focused on examining how genetic variability may contribute to opioid receptor antagonist responsivity (Chamorro et al., 2012; Ray et al., 2010), sex differences in response to opioid receptor antagonists have also been reported, with women demonstrating greater cortisol and prolactin responses, more adverse subjective effects, and better treatment outcomes than men (al'Absi et al., 2004; Epperson et al., 2010; Epstein and King, 2004; King et al., 2013; Lovallo et al., 2012b; Roche et al., 2010). Women's greater sensitivity to opioid receptor antagonists suggests an underlying sex difference in the endogenous opioid system, but the biological factors underlying these effects have not yet been characterized.

The gonadal hormones estradiol (E2) and progesterone (P4) influence endogenous opioid activity in order to regulate various reproductive functions across the menstrual cycle (MC) and estrus cycle in female mammals (Eckersell et al., 1998). In a stereotypical MC, circulating E2 levels are lowest during the early follicular phase, highest during the late follicular phase, and reach a relatively steady, intermediate level throughout the luteal phase; while P4 levels are low throughout the follicular phase, rise after ovulation, and peak during the mid-luteal phase. Across several species, E2 and P4 levels are positively associated with opioid transmission at the hypothalamic and systemic levels, and therefore may affect response to opioid receptor-binding drugs (Bernardi et al., 2006; Eckersell et al., 1998; Foradori et al., 2005; Stomati et al., 1997; Wardlaw et al., 1982; Wehrenberg et al., 1982). Despite this evidence, few studies have examined the effects of MC phase on subjective (e.g., mood) or hormonal responses to opioid receptor antagonists. Studies examining such outcome measures often enrolled women without recording MC phase, included only men in the design, or tested women in one broadly defined MC phase without hormonal confirmation, the latter of which fails to account for hormonal changes within each MC phase.

The endogenous opioid system regulates the hypothalamic-pituitary-adrenal (HPA) axis, hypothalamic—pituitary—gonadal (HPG) axis, and tuberoinfundibular dopamine (TIDA) system and thus affects the secretion of several hormones into systemic circulation, including cortisol, luteinizing hormone (LH), and prolactin, respectively. Anatomical and functional data suggest the HPA and HPG axes are tonically inhibited by endogenous opioids at the level of the hypothalamus (Baker and Herkenham, 1995; Dudas and Merchenthaler, 2004). Accordingly, opioid receptor antagonists acutely disinhibit these axes and increase the secretion of cortisol from the adrenal cortices and LH from the anterior pituitary (Mendelson and Mello, 2009). Opioids also directly regulate the hypothalamic TIDA neurons that tonically inhibit prolactin secretion from the anterior pituitary (Durham et al., 1996; Fitzsimmons et al., 1992). In support, naltrexone and nalmefene administration acutely increases circulating prolactin levels (al'Absi et al., 2004; Bart et al., 2005). While MC effects on subjective and hormonal response to naltrexone and nalmefene have not been thoroughly investigated, LH response to naloxone has been shown to be larger in late follicular and mid luteal phase women (i.e., high E2 and/or P4 level) than early follicular phase or post-hysterectomy women (i.e., low E2 and P4; Quigley and Yen, 1980; Shoupe et al., 1985).

In sum, endogenous opioid activity increases as E2 and P4 levels rise (Foradori et al., 2005; Stomati et al., 1997; Wardlaw et al., 1982; Wehrenberg et al., 1982) and, importantly, the opioid tone produced by E2 and P4 circulation may be necessary for hormonal response to opioid receptor antagonism (Shoupe et al., 1985; Stomati et al., 1997). Furthermore, hormonal response to opioid receptor antagonists may be an effective proxy measure of central endogenous opioid activity, as hypothalamic and striatal opioid transmission is positively associated with greater cortisol response to naloxone (Wand et al., 2011). Thus, in the present study, we examined whether MC phase affects acute cortisol, prolactin, LH, and subjective responses to naltrexone within women, and also compared women's responses to men's. We hypothesized that women in the luteal phase of the MC possess heightened endogenous opioid tone compared to early follicular phase women and men and, therefore, would be more sensitive to an acute dose of naltrexone and exhibit greater hormonal and subjective responses.

2. Materials and methods

2.1. Participants

Participants were recruited through advertisements on internet sites, print flyers, and by word-of-mouth referrals. Interested participants filled out an online survey and completed an initial phone screen to determine eligibility. Subjects were eligible if they were 18—35 years old, were of good general physical and mental health, had a BMI ≥ 17 or $\leq 35\,kg/m^2$ (mild thinness to moderate obesity) and did not work overnight shifts, which can affect diurnal hormone levels. Women were eligible if they had not been pregnant or lactating in the last 6 months and had a regularly occurring MC of 22—36 days (Fehring et al., 2006). Women on hormonal birth control were not considered for the study because hormonal contraceptives may affect basal cortisol levels and cortisol response to naltrexone (Roche et al., 2013). The age of 35 was chosen as the higher limit because numerous studies suggest a decline in reproductive function and increased variability in MC length and MC-related hormone levels after this age (Dunson et al.,