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Hormonal contraceptive use diminishes salivary cortisol response to psychosocial stress and naltrexone in healthy women

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ABSTRACT

The use of hormonal contraception (HC) may affect salivary cortisol levels at rest and in response to a pharmacological or stress challenge. Therefore, the current study used a secondary data analysis to investigate the effect of HC on salivary cortisol levels in response to the *mu*-opioid receptor antagonist naltrexone and a psychosocial stressor, and also across the diurnal curve. Two hundred and nine women (n = 72 using hormonal contraception; HC+) completed a two-session stress response study that consisted of a stress day, in which they were exposed to public speaking and mental arithmetic, and a rest day, in which unstimulated cortisol levels were measured to assess the diurnal rhythm. A subset of seventy women (n = 24 HC+) also completed a second study in which they were administered oral naltrexone (50 mg) or placebo in a randomized, placebo-controlled, double blind fashion. Women who were HC+ had a significantly reduced salivary cortisol response to both the psychosocial stressor ($p < 0.001$) and naltrexone ($p < 0.05$) compared to HC− women. Additionally, HC+ women had a significantly altered morning diurnal cortisol rhythm ($p < 0.01$), with a delayed peak and higher overall levels. The results of the current study confirm that HC attenuates salivary cortisol response to a psychosocial stressor and *mu*-opioid receptor antagonism, and also alters the morning diurnal cortisol curve.

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1. Introduction

The present study examined the effect of hormonal contraception (HC) on diurnal salivary cortisol secretion and acute cortisol responses to the *mu*-opioid receptor antagonist naltrexone and a psychosocial stressor. Psychosocial stressors and *mu*-opioid receptor antagonists reliability activate the hypothalamic–pituitary–adrenal axis (HPA) and increase circulating cortisol levels, but do so through separate mechanisms. For example, *mu*-opioid receptor antagonists, such as naltrexone and naloxone, are thought to disinhibit tonic endogenous opioid-mediated suppression of CRF neurons of the paraventricular nucleus of the hypothalamus (Baker and Herkenham, 1995; Mendelson and Mello, 2009). In contrast, psychosocial stressors, such as public speaking and mental arithmetic, activate diffuse corticolimbic circuitry that can relieve GABAergic inhibition or provide catecholaminergic stimulation of paraventricular CRF neurons (Herman and Cullinan, 1997; Radley and Sawchenko, 2011; Radley, 2012). Paraventricular CRF neurons also receive excitatory and inhibitory signals from the suprachiasmatic nucleus in order to regulate diurnal cortisol secretion (Kalsbeek and Buijs, 2002; Buijs et al., 2003; Dickmeis, 2009).

Mu-opioid receptor antagonism, psychosocial stressors, and measurement of diurnal cortisol levels are commonly used as probes of HPA axis function in laboratory paradigms and each has unique clinical implications in the identification and treatment of disease (al'Absi, 2006; Kiefer et al., 2006; Heim et al., 2008; Thomson and Craighead, 2008). For example, blunted cortisol response to a psychosocial stressor and attenuated diurnal levels during early abstinence are predictive of relapse in smokers (al'Absi et al., 2005; al'Absi, 2006), while naltrexone's ability to increase basal cortisol levels during treatment is associated with a reduced risk of relapse in an alcohol dependent population (Kiefer et al., 2006). Furthermore, an attenuated cortisol response to a stressor may be associated with autoimmune and inflammatory diseases (Chikanza et al., 1992; Rupprecht et al., 1995, 1997; Buske-Kirschbaum et al., 1997, 2001; Lahita, 1999). Thus, for both methodological and clinical reasons, it is important to characterize intrinsic and extrinsic factors that may impact salivary cortisol response to psychosocial stress and *mu*-opioid receptor antagonism.

Among women, one factor that may impact salivary cortisol levels is the use of HC. Women using HC have consistently demonstrated blunted salivary or free cortisol response to a psychosocial stressor

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(Kirschbaum et al., 1999; Rohleder et al., 2003; Bouma et al., 2009), but shown heightened serum total cortisol levels both diurnally and in response to a psychosocial stressor or ACTH administration (Meulenberg et al., 1987; Meulenberg and Hofman, 1990; Kuhl et al., 1993; Aden et al., 1998; Klose et al., 2007; Kumsta et al., 2007; Simunkova et al., 2008; Winkler and Sudik, 2009). However, HC's effect on diurnal salivary cortisol levels is less clear. Studies have reported HC dampening (Pruessner et al., 1997, 1999; Bouma et al., 2009), delaying and increasing (Meulenberg and Hofman, 1990), or having no effect (Wust et al., 2000) on the cortisol awakening response, as well as increasing (Meulenberg et al., 1987; Meulenberg and Hofman, 1990) or decreasing (Reinberg et al., 1996) diurnal salivary cortisol levels.

It has been speculated that the primary factor underlying HC-mediated changes in cortisol levels is increases in circulating corticosteroid-binding globulin (CBG; Kirschbaum et al., 1999; Kumsta et al., 2007; Hellhammer et al., 2009; Kudielka et al., 2009). CBG is a glycoprotein that transports cortisol to target tissues and regulates its clearance rates, with ~95% of circulating cortisol being bound to CBG or serum albumin under normal conditions (Lewis et al., 2005). Hormonal contraception that contains either an estrogen or progesterone increases circulating CBG levels (Durber et al., 1976; Wiegratz et al., 2003), which subsequently increases the ratio of total to free cortisol by both increasing CBG-bound cortisol and decreasing free cortisol levels (Meulenberg et al., 1987; Meulenberg and Hofman, 1990; Wiegratz et al., 1995, 2003; Klose et al., 2007). However, estradiol and progesterone have been shown to directly alter endogenous opioid (Foradori et al., 2002, 2005; Smith et al., 2006), CRF neuron (Chen et al., 2008; Lalmansingh and Uht, 2008; Zhu and Zhou, 2008) and HPA axis activity (Kirschbaum et al., 1996; Kudielka et al., 1998; Thammacharoen et al., 2009), all of which could feasibly contribute to differences in diurnal cortisol secretion and stress-induced salivary cortisol response.

To date, no studies have examined the effects of HC on salivary cortisol response to *mu*-opioid receptor antagonism. Therefore, the primary goal of the current study, which was a secondary data analysis, was to replicate prior findings that HC use impacts salivary cortisol response to a psychosocial stressor and to extend these findings by examining naltrexone responsivity. Based on the results of previous stressor studies, we hypothesized that women using HC (HC+) would demonstrate a blunted salivary cortisol response to both a psychosocial stressor and naltrexone in comparison to women not using HC (HC−). Since blood sampling was not included in the original study design, CBG levels could not be ascertained. Instead, subjective response to both stimuli and heart rate response to the stressor were examined as secondary measures to help elucidate whether HC is exerting its effects through peripheral or central mechanisms. For example, heart rate is under the control of the autonomic nervous system, which, like the HPA axis, is regulated by the hypothalamus (Gunnar and Quevedo, 2007). Therefore, if HC was directly affecting hypothalamic reactivity we would expect both cortisol and heart rate response to a stressor to be altered. However, we expected that a blunted cortisol response to a stressor or naltrexone would be primarily due to HC's effects on peripherally circulating CBG levels rather than changes in HPA axis or central opioidergic function. Thus, we hypothesized that subjective and heart rate response to the stimuli would not differ between HC+ and HC− women. Finally, given the inconsistent results of previous studies examining unstimulated, basal cortisol levels, we explored whether HC affects the diurnal cortisol rhythm.

2. Methods

2.1. Participants

Participants were women who were taking part in the Oklahoma Family Health Patterns Project (OFHP), previously described elsewhere (Lovallo et al., 2010, 2012a, 2012b). Subjects signed a consent form approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and the Veterans Affairs Medical Center, Oklahoma City, OK, USA, and received financial compensation for participating.

Two hundred and nine women (n = 72 using hormonal contraception; HC+) participated in the stressor study and seventy of those women (n = 24 HC+) also completed the naltrexone study (Table 1). Inclusion and exclusion criteria for both studies were previously described in detail (Lovallo et al., 2012a, 2012b). In brief, all participants were in good physical health, between the ages of 18 and 30 years, had BMI between 18.5 and 29 kg/m^2, were not using prescription medications other than hormonal contraceptives, had daytime job or school schedules with a normal nighttime sleep pattern, and had no reported history of serious medical or psychiatric disorder. Exclusion criteria were: diagnosis of a current or past Axis I disorder [other than past depression (>60 days prior)], history of alcohol or drug dependence, met any criteria for substance abuse within the previous 2 months, or a positive urine drug screen, pregnancy test, or breath-alcohol test on days of testing. Smoking and smokeless tobacco use were not exclusionary. Thirty subjects (14%) reported using tobacco (Table 1). Smokers were allowed a cigarette immediately prior to the start of the protocol to reduce confounds of tobacco withdrawal symptoms on study assessments; no smoking was allowed during the sessions.

Hormonal contraceptive use was determined based on a health history and current medications questionnaire taken during screening and reconfirmed on days of testing. Based on this self-report, women were divided into 2 groups, those who reported current use of HC (HC+, including birth control pills, patch, hormonal IUD, or ring) and those who reported no current use (HC−).

2.2. Study design and procedure

2.2.1. Stressor study

The procedure for the stressor study was previously described in detail (Lovallo et al., 2012a). Subjects participated in two sessions that consisted of either stress or rest protocols, in a fixed order. To maximize stress response, the first session always consisted of the stress protocol and the rest day was the second session. Prior to the start of the stress session, subjects self-reported the start date of their most recent menstrual cycle. The sessions began at either 0900 h (n = 99) or 1300 h (n = 110), and subjects were tested at the same time for both sessions. These scheduling block options were offered to facilitate enrollment and was chosen because they would not confound within-subject difference score analyses of cortisol response. Subjects received a standardized snack upon arrival at the laboratory account for the effects of blood glucose levels on cortisol secretion (Dallman, 2003).

The stress protocol was 105 min in total, and consisted of a 30 min baseline period, a 45 min stress test, and a 30 min recovery period. During the baseline period, the subject relaxed and read magazines. The stress test included public speaking (30 min) followed by a mental arithmetic (15 min) task. The speech task consisted of three prepared speeches on randomly generated topics, given consecutively in front of a video camera and a white-coated experimenter holding a clipboard. The mental arithmetic task consisted of three consecutive 5 min periods, in each of which the subject was given a three-digit number (e.g., 137), told to sum the three digits (11), then add aloud that total to the original number (148), and to proceed in that fashion until told to stop.

The subject provided five saliva samples during the stress protocol: at 10 and 20 min of the baseline period (Baseline 1 and Baseline 2), at 15 and 30 min of the stress test (Stress 1 and Stress 2), and at the end of the 30 min recovery period (Recovery). To assess subjective response to the stress protocol, subjects rated their moods at each saliva sample