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Do sex hormones influence emotional modulation of pain and nociception in healthy women?

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ABSTRACT

Sex hormones may contribute to inter- and intra-individual differences in pain by influencing emotional modulation of pain and nociception. To study this, a well-validated picture-viewing paradigm was used to assess emotional modulation of pain and the nociceptive flexion reflex (NFR; physiologic measure of nociception) during mid-follicular, ovulatory, and late-luteal phases of the menstrual cycle in healthy normally cycling women ($n = 40$). Salivary estradiol, progesterone, and testosterone were assessed at each testing session. Emotional modulation of pain/NFR did not differ across menstrual phases, but low estradiol was associated with weaker emotional modulation of NFR (during all phases) and emotional modulation of pain (ovulatory and late-luteal phases). Given evidence that a failure to emotionally modulate pain might be a risk factor for chronic pain, low estradiol may promote chronic pain via this mechanism. However, future research is needed to extend these findings to women with disturbances of pain, emotion, and/or sex hormones.

1. Introduction

Compared to men, women have a higher prevalence of many chronic pain conditions (e.g., fibromyalgia, migraine) and a greater sensitivity to noxious stimuli (e.g., Fillingim, 2000; Riley, Robinson, Wise, Myers, & Fillingim, 1998; Unruh, 1996). Moreover, some clinical pain varies across the menstrual cycle (Craft, 2007; LeResche, Mancl, Sherman, Gandara, & Dworkin, 2003; Straneva et al., 2002). Thus when taken together, inter- and intra-individual differences in sex hormones may contribute to pain and pain modulation in humans (Craft, 2007).

Much of the research examining the relationship between hormones and human pain have used menstrual phase as a proxy for hormone levels without directly measuring them (e.g., Riley, Robinson, Wise, & Price, 1999; Sherman & LeResche, 2006). For example, estradiol and progesterone are relatively low during the early-follicular phase (days 1–5 of a 28 day menstrual cycle) and higher during the mid-luteal phase (days 17–24). Estradiol peaks prior to ovulation (day 14) triggering a rapid surge (and immediate return to baseline) in luteinizing hormone (LH) and follicle stimulating hormone (FSH). Despite this general pattern, there can be tremendous inter- and intra-phase variability, as well as inter-individual variability in sex hormones (Vitzthum, 2009).

Surprisingly, few studies have actually measured hormone levels and responses to well-controlled pain stimuli to directly assess the relationships between hormones and nociceptive processing. Moreover, conclusions are difficult to draw from these studies because the direction of the relationships is not always consistent, and there have been several null findings (e.g., Fillingim et al., 1997; Klatzkin, Mechlin, & Girdler, 2010; Okifuji & Turk, 2006; Ring, van Zanten, & Kavussanu, 2009; Soderberg, Poromaa, Nyberg, Backstrom, & Nordh, 2006; Stening et al., 2007; Teepker, Peters, Vedder, Schepelmann, & Lautenbacher, 2010). Variability across studies may reflect the complex effects of hormones (e.g., sometimes pronociceptive, sometimes antinociceptive), but may also stem from low statistical power because many had small sample sizes and used low-powered analytic procedures (e.g., zero-order correlations).

Additionally, most studies have focused on static measures of pain processing (e.g., pain threshold/tolerance), rather than dynamic measures of pain modulation. Indeed, pain is determined not only by the amount of nociceptive input, but also by central modulatory processes. Some of these processes inhibit pain, whereas others facilitate (disinhibit) it (Fields, Basbaum, &

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Heinricher, 2006; Millan, 2002). As a result, experienced pain is the net effect of nociceptive input, inhibitory processes, and facilitatory processes. Recent thinking is that risk for some chronic pain may be determined by individual differences in central pain modulation (Edwards, 2005). As evidence for this, several chronic pain conditions are associated with reduced descending inhibition (Lautenbacher & Rollman, 1997; Pielsticker, Haag, Zaudig, & Lautenbacher, 2005; Yarnitsky, 2010). Even more convincing is a prospective study showing that disrupted preoperative pain inhibition predicts the development of chronic post-thoracotomy pain (Yarnitsky et al., 2008). Thus, given the importance of pain modulation in the risk for chronic pain, it is important to examine whether hormones are related to pain modulation.

To the best of our knowledge only three studies have examined the relationship between sex hormones and pain modulation. Two used a method of assessing pain inhibition known as conditioned pain modulation (CPM) that involves applying a tonic noxious stimulus to one part of the body to inhibit pain evoked at a distal body location. Both found that pain inhibition was the strongest during ovulation (Rezaii, Hirschberg, Carlström, & Ernberg, 2012; Tousignant-Laflamme & Marchand, 2009), suggesting that weaker pain inhibition during other phases (e.g., follicular, luteal) may promote pain. Both studies measured several sex hormones (e.g., estradiol, progesterone, testosterone, LH, FSH), but only Tousignant-Laflamme and Marchand (2009) found a relationship: higher progesterone was associated with greater CPM-related inhibition during the ovulatory phase only.

The third study, conducted by our laboratory, examined emotional modulation of pain across the mid-follicular (days 5–8) and late-luteal (1–6 days prior to menses) phases in 41 healthy women (Rhudy & Bartley, 2010). An emotional picture-viewing paradigm (Emotional Controls of Nociception; ECON) was used to manipulate emotion and suprathreshold electrocutaneous stimuli were delivered over the sural nerve to evoke pain and the nociceptive flexion reflex (NFR; a physiological correlate of spinal nociception). We reasoned that emotional modulation of pain might be even more sensitive to hormone influences than CPM-inhibition because supraspinal regions involved with emotional modulation circuits show sex differences in structure and function (e.g., Cahill, 2006; Tershner, Mitchell, & Fields, 2000; Zubieta et al., 2002) and are affected by sex hormones (e.g., Smith, Zubieta, & delCarmen, 1998; Vincent & Tracey, 2010). Consistent with prior studies (e.g., Rhudy, Williams, McCabe, Nguyen, & Rambo, 2005; Rhudy, Williams, McCabe, Russell, & Maynard, 2008), pain and NFR were modulated according to an emotional valence linear trend (pain and NFR were highest during unpleasant pictures and lowest during pleasant pictures), but this modulation did not vary across the menstrual phases (Rhudy & Bartley, 2010). Unfortunately, we did not assess ECON during the ovulatory phase, nor did we directly assess sex hormones. Given these limitations, it is yet unclear whether sex hormones influence emotional modulation of pain/NFR.

To address these limitations, the present study assessed ECON in 40 healthy, normally cycling women during the mid-follicular (days 5–8), ovulatory (within 48 h following LH surge), and late-luteal (1–6 days prior to menses) phases of the menstrual cycle. Salivary estradiol, progesterone, and testosterone were collected at each testing session. Statistically powerful linear mixed models were used to analyze the data. Based on studies of CPM-inhibition (Rezaii et al., 2012; Tousignant-Laflamme & Marchand, 2009), we predicted that emotional modulation of pain and NFR would be strongest during the ovulatory phase. But, given the lack of research on hormones and emotional modulation of pain/NFR, we did not make directional hypotheses for these relationships. However, estradiol might play a particularly important role because it affects mu opioid binding in regions important for emotion and pain modulation (e.g., amygdala, hypothalamus, nucleus accumbens) (Smith et al., 2006). Because we assessed subjective and physiological measures of emotional valence (i.e., valence/pleasure ratings, corrugator EMG) and emotional arousal (i.e., arousal ratings, skin conductance response [SCR]) in response to pictures, an ancillary goal was to examine the relationships between sex hormones and these emotional reactions.

2. Methods

2.1. Participants

Forty healthy, regularly cycling women were recruited from the surrounding community by radio/newspaper advertisement, flyers, online advertisements, and referrals from OB/GYN doctors. Participants were excluded for being less than 18 years of age, factors that could influence naturally occurring hormone levels (i.e., being menopausal or post-menopausal, use of hormone preparations in the last 6 months, failure to regularly cycle, hysterectomy, polycystic ovarian syndrome, endometriosis, pregnant or trying to become pregnant, pregnant in the last six months or currently breastfeeding), chronic health conditions (i.e., history of cardiovascular, neuroendocrine, or neurological disorders, Raynaud's disease, hypertension), history of chronic pain, use of medications that could influence testing (i.e., current analgesic, antidepressant, or anxiolytic medication use), apparent cognitive impairment, current diagnosis of premenstrual dysphoric disorder (PMDD), or body mass index > 35 (due to difficulty getting a nociceptive reflex in persons with high adiposity). Participants were also excluded if they met criteria for any current Axis I pathology as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient Version (SCID-I/NP) (First, Spitzer, Gibbons, & Williams, 2002). Participants were provided an honorarium (up to $375) at the end of the experiment or upon withdrawal from the study. In general, participants were white (80%, $n = 32$), single (47.5%, $n = 19$), and employed at least part-time (65%, $n = 26$), with an average age of 29 years ($SD = 8.57$). Most were well educated (mean years of education = 15 years, $SD = 2.48$). Average body mass index (BMI) was 24.56 ($SD = 3.96$) and average blood pressure was 108/68 ($SD_{sys} = 11.02$, $SD_{dia} = 8.78$).

2.2. Apparatus, electrode application, and signal acquisition

A computer running LabVIEW software (National Instruments, Austin, TX) equipped with dual monitors and A/D board (National Instruments, PCI-6036E) controlled all stimuli, questionnaire presentation, and data acquisition. Physiological signals were amplified and filtered online using Grass Technologies (West Warwick, RI) Model 15LT amplifiers (with AC Modules 15A54 and DC Modules 15A12). Signals and experimental timing were monitored by an experimenter in an adjacent room by use of a 17 in. flat panel monitor. Picture stimuli and most questionnaires were presented by a projector onto a large screen positioned approximately 2 m in front of the participant, and sound attenuating headphones and a video camera allowed the experimenter to communicate with and monitor the participant from an adjoining room.

Electrocutaneous trains of five 1 ms rectangular wave pulses at 250 Hz (experienced as a single stimulus) were delivered to the left ankle over the retromalleolar pathway of the sural nerve by use of a Digitimer stimulator (model DS5A; Hertfordshire, England) and bipolar stimulating electrode (Nicolet, Madison, WI; 30 mm inter-electrode distance). A computer controlled the timing of the electric stimulations. The maximum stimulation intensity was set at 50 mA to ensure participant safety. Resting blood pressure was recorded prior to testing using a Critikon Dinamap PRO 100 Monitor (Tampa, FL) three times at 3-min intervals. A mechanical scale with attached height rod (Detecto, Webb City, MO) was used to assess weight and height for BMI.

Electromyographic (EMG) signals for biceps femoris muscle (i.e., hamstring muscle to assess NFR) and corrugator muscle (i.e., eyebrow muscle to assess facial affect) activity were recorded using Ag–AgCl electrodes. Biceps femoris EMG was recorded from two 11 mm disc electrodes (F-E9-40-5; Grass Technologies) placed 10 cm superior to the popliteal fossa, amplified 20,000×, bandpass filtered (10–300 Hz), and rectified online. Corrugator EMG was recorded from two 5 mm miniature electrodes (F-E9M-40-5; Grass Technologies) affixed over the left corrugator muscle of the eyebrow, amplified 20,000×, bandpass filtered (30–1000 Hz), and rectified online. An 11 mm ground electrode was placed over the lateral epicondyle of the femur. To apply EMG and stimulating electrodes, the skin was initially cleaned with alcohol, slightly abraded using NuPrep gel (Weaver and Company, Aurora, CO) to attain impedances below 5 kΩ, and then conductive gel (EC60, Grass Technologies) was applied. Skin conductance response was measured from two 11 mm electrodes filled with isotonic paste (EC33, Grass Technologies) affixed to the volar surface of the index and middle fingers of the non-dominant hand after the participant's skin had been washed with soap and water and dried. All physiological signals were sampled at 1000 Hz.