Endogenous Inhibition of the Nociceptive Flexion Reflex (NFR) and Pain Ratings During the Menstrual Cycle in Healthy Women

Emily J. Bartley, M.S. · Jamie L. Rhudy, Ph.D.

Published online: 31 January 2012
© The Society of Behavioral Medicine 2012

Abstract

Background The menstrual cycle influences pain, with symptoms often increasing during the premenstrual (late-luteal) phase. Deficiencies in endogenous inhibition of afferent nociception at the spinal level might contribute to menstrual phase-related changes in pain.

Purpose This study assessed whether conditioned pain modulation (CPM) of spinal nociception differs between mid-follicular and late-luteal phases.

Methods CPM was evoked by a blood pressure cuff affixed to the right forearm and inflated to induce ischemia in 41 healthy women during both menstrual phases. Suprathreshold electric stimuli were delivered to the left sural nerve to evoke pain and the nociceptive flexion reflex (NFR) before, during, and after forearm ischemia.

Results Forearm ischemia produced CPM of electrocutaneous pain and NFR, but inhibition did not differ across mid-follicular and late-luteal phases.

Conclusions Mechanisms contributing to changes in experimental pain across mid-follicular and late-luteal phases in healthy women are not due to deficits in CPM of spinal nociception.

Keywords Menstrual cycle · Conditioned pain modulation · Nociceptive flexion reflex · Pain · Descending modulation

Introduction

While pain impacts both sexes, evidence supports a clear female predominance [1], with women reporting clinical pain more frequently than men [2–4], and experiencing increased sensitivity to experimental pain stimuli [3, 5–8]. Further, clinical pain has been noted to increase during the late-luteal (premenstrual) phase of the menstrual cycle [9–15]. Although multiple factors may contribute to enhanced clinical pain and pain sensitivity in women, one mechanism that may account for these effects is endogenous pain inhibitory processes. Indeed, deficiencies in inhibitory processes may serve as a diathesis for developing chronic pain [16], or could initiate and maintain it [17].

A common method of assessing endogenous pain inhibition in humans is through conditioned pain modulation (CPM). CPM involves the application of a tonic painful stimulus (i.e., conditioning stimulus) that inhibits nociception (pain signaling) evoked by a phasic painful stimulus (i.e., test stimulus) applied at a distant body site. Thus, CPM is a process by which pain inhibits other pain. Animal studies indicate that CPM is mediated by a descending (brain-to-spinal cord) mechanism involving the subnucleus reticularis dorsalis [18] that inhibits the activity of nociceptive neurons in the spinal cord dorsal horn [19]. Deficits in CPM inhibition have been found in chronic pain conditions where dysfunctional CNS pain processing is believed to play a role, including fibromyalgia [20–22], temporomandibular disorder [23], irritable bowel syndrome [23], and chronic tension-type headache [24]. Further, a recent meta-analysis noted attenuated CPM in women relative to men, suggesting that impairments in CPM inhibition may contribute to the increased prevalence of pain among women and perhaps the increased clinical pain during the late-luteal (premenstrual) phase of the menstrual cycle [25].

There is a substantial literature investigating the effects of CPM on pain in clinical and healthy populations; however, only one study has assessed CPM across different menstrual phases. Tousignant-Laflamme and Marchand [26] examined the effect of a cold pressor conditioning stimulus on pain...
evoked by a thermal heat test stimulus in 32 healthy women. The authors found that CPM inhibition was greater during the ovulatory phase (days 12–14) relative to the menstrual phase (days 1–3), with a trend (p=0.08) for the ovulatory phase to be greater than the mid-luteal phase (days 19–23). Mid-luteal and menstrual phases were not significantly different from each other. The authors did not assess CPM inhibition during the late-luteal phase, a period when enhanced pain is often observed [9–14].

While it is implied that brain-to-spinal cord circuits were engaged to inhibit spinal nociception in the study by Tousignant-Laflamme and Marchand, this was not directly tested since they only assessed subjective pain outcomes. There are multiple pathways by which nociceptive processes can be modulated. For example, incoming pain signals can be modulated at the spinal level, the supraspinal (brain) level, or both (see Fig. 1). Given evidence that measures of pain and spinal nociception can diverge (for a review [27]), at this time, it is unclear whether menstrual phases differentially engage descending brain-to-spinal cord circuits to modulate nociception at spinal levels. Addressing this issue can help clarify the mechanisms that contribute to pain across the menstrual cycle in women.

Thus, the purpose of the present study was to determine whether the brain-to-spinal cord inhibition of spinal nociception was influenced by the menstrual cycle when comparing across the mid-follicular and late-luteal phases. The results of the Tousignant-Laflamme and Marchand study were not published at the time this study was being conducted; therefore, our choice of menstrual phases was based on phases previously shown to produce robust changes in pain sensitivity [28–30]. Pain ratings and nociceptive flexion reflex (NFR) magnitudes in response to electrocutaneous stimuli were measured before, during, and after forearm ischemia. We hypothesized that CPM inhibition of pain and NFR would be attenuated (deficient) during the late-luteal phase of the menstrual cycle as compared to the mid-follicular phase. To our knowledge, this is the first study to assess CPM across the mid-follicular and late-luteal phases. Further, no study to date has measured CPM effects on the spinally mediated NFR across the menstrual cycle. The NFR is a physiological measure of spinal nociceptive processes previously shown to be modulated by CPM [31]; thus, measurement of NFR provides a means to assess menstrual cycle-related changes in CPM inhibition of spinal nociception [27].

These data were collected as part of a larger study on the menstrual cycle and pain. Results from other procedures (e.g., emotional modulation of pain and NFR) in the parent study have been reported elsewhere [32, 33]. The data in this report have only been previously presented at a conference [34].

Methods

Participants

Participants were recruited from the University of Tulsa psychology subject pool, as well as the surrounding community by radio/newspaper advertisement, flyers, and email distribution. Participants were excluded for: <18 years of age; menopausal or postmenopausal; use of hormone preparations in the last 6 months; failure to regularly cycle in the 2 months prior to study inclusion; history of hysterectomy; pregnant or trying to get pregnant; pregnant in the last 6 months or currently breastfeeding; body mass index >35 (due to difficulty getting a nociceptive flexion reflex); history of cardiovascular, neuroendocrine, or neurological disorders; Raynaud’s disease; hypertension; history of chronic pain; current opioid, antidepressant, or anxiolytic medication use; or recent psychological

Fig. 1 Illustration of pain modulatory processes. Noxious events activate primary afferents that carry the pain signal to the dorsal horn of the spinal cord. The message is then relayed to supraspinal (brain) centers by ascending tracts. Pain modulation can occur via descending brain-to-spinal cord circuitry, by supraspinal circuitry (e.g., cortico-cortical mechanisms), or both. To determine whether pain signaling is modulated at spinal levels, a measure of spinal nociception (e.g., the nociceptive flexion reflex) must be measured.
Menstrual Cycle Monitoring and Phase Determination

Menstrual cycles were monitored using the Prospective Record of the Impact and Severity of Menstrual Symptoms (PRISM) [36]. The PRISM calendar contains affective (e.g., depressed), behavioral (e.g., insomnia), and physical (e.g., breast tenderness) symptoms that are rated daily for severity (absent, mild, moderate, severe). Participants completed the calendars daily for three menstrual cycles. To discourage retrospective reporting, participants were asked to mail in calendars on a weekly basis. Pain testing sessions were scheduled during the mid-follicular and late-luteal phases of the participant’s menstrual cycle during cycles 2 and 3. Testing order was counterbalanced between subjects. The mid-follicular phase was defined as days 5–8 following menses onset, while the late-luteal phase was identified as days 1–6 preceding menses [or approximately 9 to 11 days following the luteinizing hormone (LH) surge that triggers ovulation]. Verification of ovulation was obtained from an early urine test for ovulation [or approximately 9 to 11 days following the luteinizing hormone (LH) surge that triggers ovulation]. Verificatio

Electrode Application and NFR Signal Acquisition

Sampling rate of biceps femoris electromyography (EMG) for NFR recording was set at 1,000 Hz, and signals were collected/filtered using a Grass Instruments Model 15LT Bipolar Amplifier with one Dual DC (15A12) and two Quad AC (15A54) modules. All recording electrodes were Ag–AgCl. To apply all EMG and stimulating electrodes, the skin was first cleaned with alcohol, slightly abraded using NuPrep gel to achieve impedances below 5 KΩ, and then electrodes were filled with conductive gel (EC60, Grass Instruments). NFR recording was assessed by attaching two electrodes over the biceps femoris muscle of the left leg 10 cm superior to the popliteal fossa, and a common ground electrode was placed over the lateral epicondyle of the left femur. The raw biceps femoris EMG was amplified, bandpass filtered (10–300 Hz), and rectified.

Nociceptive Outcomes

Subjective Pain Assessment

Following each electric stimulus, a vertically oriented computer-presented numerical rating scale (NRS) was administered [37, 38]. The scale ranged from 0 to 100 with the following labels: 0 (no sensation), 1 (just noticeable), 25 (uncomfortable), 50 (painful), 75 (very painful), and 100 (maximum tolerable) [38–41]. Using a computer mouse, participant responses were made by moving an indicator to a position along the line that corresponded to their rating and submitting their answer by pressing a button.

NFR Magnitude Assessment

The nociceptive flexion reflex (NFR) is a spinally mediated withdrawal reflex elicited by activation of Aδ fibers and
following noxious stimulation. Suprathreshold electrocutaneous stimulations delivered during CPM testing were set at 120% NFR threshold. Therefore, prior to CPM testing, the NFR threshold was assessed. To assess NFR threshold, trains of five 1-ms rectangular wave pulses at 250 Hz (i.e., 3 ms interstimulus interval) were delivered to the sural nerve with a varying intertrain interval of 8–12 s to reduce stimulus predictability. The first train started at 0 mA (current) and was increased in steps of 1.5 mA until an NFR was detected. The stimulus intensity was then decreased in 0.75 mA steps until an NFR was no longer observed. This up-down staircase process was repeated two more times, but with the use of 0.5 mA steps. NFR threshold was defined as the average stimulation intensity (in milliamperes) of the last two peaks and troughs of the up-down staircase procedure.

During CPM testing, NFR magnitude was used as the index of spinal nociception, because NFR magnitude correlates highly with subjective pain ratings [27, 42], as well as activity of nociceptive neurons in the dorsal horn [43]. Thus, we expected NFR magnitude to be reduced during forearm ischemia as a result of CPM inhibition. NFR magnitude was scored from a 90–150-ms interval following the electric stimulus to reduce potential contamination by the nonnociceptive RII reflex, startle responses, and/or voluntary movements [44]. NFR magnitude was put into Cohen’s d units ($d = (\text{mean EMG of 90–150 ms poststimulation interval} - \text{mean EMG of 60 ms prestimulation interval}) / \text{average SD of EMG from pre- and poststimulation intervals}$). This method was chosen because we have shown that it produces a stronger correlation with pain report (i.e., external validity coefficient) than other NFR scoring methods (e.g., mean EMG) [42, 45]. For comparison to other NFR studies though, we also present the baseline adjusted mean EMG values (i.e., mean EMG 90–150 ms poststimulation interval – mean EMG 60 ms prestimulation interval) which are in units of microvolts.

Assessment of Conditioned Pain Modulation

The procedures used during CPM were adapted from the 15-min testing procedure (5 min per CPM phase) used by France and Suchowiecki [46], but shortened to 6 min (2 min per CPM phase). CPM involves the application of a painful conditioning stimulus that activates descending inhibitory processes to dampen pain assessed from a distant (heterotopic) body site. For the present study, forearm ischemia was used as the tonic conditioning stimulus and electrical stimulation was used as the phasic test stimulus [39, 46]. To induce ischemia, participants conducted hand exercises using a dynamometer at 50% their maximal effort at a rate of one compression per second for 2 min. After the handgrip exercises, the arm was elevated for 15 s for exsanguination. A blood pressure cuff was then affixed to the biceps of the arm, inflated to 220 mmHg to occlude blood flow, and then participants rested their arm on the chair. The blood pressure cuff was kept inflated for 2 min. The distant pain was assessed by delivering suprathreshold electric stimuli (intensity=120% NFR threshold) to the sural nerve with a 15–25-s variable interstimulus interval. Four stimuli were delivered −4 to −2 min prior to ischemia, four stimuli were delivered during the 2 min of ischemia, and four stimuli were delivered 2 to 4 min post-ischemia. Each stimulus consisted of a train of five 1-ms square wave pulses at 250 Hz (analogous to stimuli delivered during NFR threshold testing). The numerical pain rating scale described above was administered following each electric stimulus to assess pain. Biceps femoris EMG was recorded throughout to assess NFR magnitude. Following the CPM procedure, an NRS as previously described was administered to participants with instructions to rate the pain in response to the blood pressure cuff on their arm (i.e., forearm ischemia pain).

Procedure

All procedures were fully approved by the University of Tulsa ethics review board. Interested participants were administered a brief phone screen to evaluate inclusion/exclusion criteria. Potentially eligible participants attended an initial laboratory visit during which a thorough overview of the study was provided, informed consent was obtained, and then a comprehensive assessment of inclusion/exclusion criteria was conducted. If deemed eligible, participants were trained to monitor their menstrual cycle and then randomly assigned to a testing order (i.e., mid-follicular/late-luteal vs. late-luteal/mid-follicular). Participants were then asked to track their menstrual phases for three cycles. Cycle 1 was used to establish cycle length and ovulation timing. Experimental pain testing occurred in cycles 2 and 3 and testing order was counterbalanced between subjects. Due to potential diurnal variations in pain processing, testing sessions were scheduled at approximately the same time of day.

Upon arrival at the laboratory for a testing session, a complete overview of the procedures was provided, followed by review of informed consent and health status. Afterwards, subjects were provided instruction on the numerical rating scale for rating pain. Next, mechanical pressure–pain thresholds were assessed from six body sites (data presented elsewhere) [32], followed by psychophysiological sensor application. NFR threshold was then assessed to determine the level of stimulation to use during CPM testing. Next, a set of 24 emotionally charged pictures that varied in content (erotica, neutral, mutilation) was presented to allow for the assessment of emotional modulation of pain (part of another study aim, data presented elsewhere) [33]. We have previously shown that the effects of emotion.
induction only persist for a few seconds [47]; nonetheless, a 10-min break was given before CPM testing to minimize any emotional carry-over effects. During the first part of the break, participants filled out questionnaires about their menstrual symptoms. After the break, CPM testing occurred. The session concluded with the assessment of electrocutaneous pain threshold/tolerance and ischemia pain threshold/tolerance (reported elsewhere) [32]. At the end of the session, participants were instructed to continue monitoring their menstrual phases until three cycles were completed.

Preliminary Analyses and Data Analysis

Analyses of the parent study [32, 33] found that menstrual and affective symptoms did not differ across menstrual phases, except that headaches were more severe during the mid-follicular phase and breast tenderness was more severe during the late-luteal phase. Therefore, any menstrual phase effects noted in CPM are unlikely to be due to fluctuations during the late-luteal phase. Therefore, any menstrual phase effects noted in CPM are unlikely to be due to fluctuations in menstrual and affect variables.

The MIXED procedure in SPSS 14.02 (IBM Corporation; Somers, NY) [48] was used for all analyses because: (1) cases with missing data on the within-subject variables are not excluded, thereby taking advantage of all data points, (2) statistical power is increased because cases with missing data are not excluded and because maximum likelihood is used instead of the general linear model, and (3) the variance–covariance structure can be fit to the data rather than being fixed to compound symmetry (as is true for general linear model). The error structure was modeled as AR1, and subject ID was used as the grouping variable. These analyses entered menstrual phase (mid-follicular vs. late-luteal) and CPM phase (pre-ischemia, ischemia, post-ischemia) as nominal within-subjects variables; therefore, most models were 2 (menstrual phase)×3 (CPM phase) ANOVAs. Counterbalance order (mid-follicular/late-luteal vs. late-luteal/mid-follicular) was also entered as an independent variable in all analyses to test for potential order effects, but it was nonsignificant in all models and dropped. The SPSS MIXED procedure uses Satterthwaite estimation for the denominator degrees of freedom (df) which produces noninteger values that vary from analysis to analysis. For ease of reporting, these dfs were rounded to the nearest integer. Cohen’s d was reported as the effect size for comparisons between means. Significance was set at p<0.05 (two tailed). Some women were tested outside of the target windows for mid-follicular (days 5–8) and late-luteal (days 1–6 preceding menses) phases (see “Results” section for descriptive data); therefore, CPM data were analyzed by: (1) including all 41 participants (even if testing occurred outside of the window) and (2) restricting data to only those testing sessions that occurred in the target windows. However, both approaches resulted in similar conclusions; therefore, only data from the total sample (N=41) are presented.

Results

Participant Characteristics

All participants had regular menstrual cycles ranging from 21.67 to 37.77 days (M=28.98, SD=3.28). Average luteal phase length was 14.74 days (SD=3.48) as calculated from the date of positive LH surge until 1 day preceding menses onset. Thirty-four women completed both testing sessions and 7 completed one session. Of the seven women who failed to complete both testing sessions, three completed the mid-follicular phase while four completed the late-luteal phase. Reasons given for completing only one session were: scheduling, health problems unrelated to menstrual cycle, and procedures too painful.

Twenty-one females attended their first testing session during their mid-follicular phase and 20 attended their first testing session during their late-luteal phase. Of the 37 women who completed the mid-follicular testing session, 33 (89%) were tested during days 5–8 (M=7.54, SD=1.17). The average testing day for the other four women was day 9.5 (range=9–10) due to their menses lasting longer than 8 days. Thus, their testing session still occurred during the mid-follicular phase even though they were tested outside of the targeted window of days 5–8.

Of the 38 women who completed the late-luteal testing session, 30 (79%) were tested 1–6 days preceding menses (M=4.84, SD=3.24). The average testing day for the other eight women was 9.25 days preceding menses (range=7–15). Difficulty in assessing women during the late-luteal phase stemmed from problems predicting the onset of menses from prior cycles and prior LH surges.

Conditioned Pain Modulation

NFR Threshold

NFR threshold did not differ across the mid-follicular (M=9.22, SD=4.02) and late-luteal (M=9.86, SD=5.25) menstrual phases [F(1, 30)=0.13, p=0.72, d=0.14]; thus, the suprathreshold stimulation intensity used during CPM did not differ by phase.

Forearm Ischemia Pain

Results from the numerical rating scale indicated that participants rated the forearm ischemia as painful during both menstrual phases (mid-follicular—M=67.03, SD=22.27; late-luteal—M=71.68, SD=20.50), signifying that the task
was successful in evoking tonic forearm ischemia pain. The main effect of menstrual phase was significant, \(F(2, 862) = 44.59, p < 0.001\), indicating that participants rated the ischemia as slightly more painful during the late-luteal phase than the mid-follicular phase \(d = 0.22\).

**CPM of Electrocutaneous Pain Ratings**

Ratings of electrocutaneous stimuli are presented in Fig. 2a. Ratings were significantly lower during the late-luteal phase relative to the mid-follicular phase \(d = 0.18\), as indicated by a significant main effect of menstrual phase \([F(1, 85)] = 6.36, p = 0.014\). Further, the main effect of CPM Phase was also significant \([F(2, 495)] = 12.01, p < 0.001\). As expected, ratings were lower during ischemia relative to pre-ischemia \((p < 0.05, d = 0.10)\), but ratings were also lower during post-ischemia relative to pre-ischemia \((p < 0.001, d = 0.28)\) and ischemia \((p < 0.001, d = 0.17)\) phases. These inhibitory effects were not influenced by the menstrual cycle \([menstrual phase \times CPM phase interaction, F(2, 475) = 1.31, p = 0.272]\). Together, this implies that CPM inhibition was engaged by ischemia which persisted during the post-ischemia phase (after effects), but these effects did not differ across menstrual phases.

**CPM of NFR Magnitudes**

NFR magnitudes are presented in Fig. 2b. For comparison, mean EMG values for NFR are presented in Table 1. A significant main effect of CPM phase was found \(F(2, 420) = 11.55, p < 0.001\). Specifically, reflex magnitudes were smaller during ischemia, relative to pre-ischemia \((p < 0.001, d = 0.34)\) and post-ischemia \((p < 0.001, d = 0.29)\), but there were no differences between pre-ischemia and post-ischemia \((p = 0.338, d = 0.06)\). This inhibitory effect was not influenced by the menstrual cycle \([menstrual phase \times CPM phase interaction, F(2, 357) = 0.65, p = 0.52]\). There was also no main effect of menstrual phase \([F(1, 206) = 0.24, p = 0.62]\). Together, this indicates that CPM inhibition of spinal nociception was engaged by ischemia and then returned to baseline values during post-ischemia, but these effects did not differ by menstrual phase.

**Discussion**

The purpose of the current study was to assess the effect of the menstrual cycle on endogenous inhibition of spinal nociception (assessed from NFR) and pain perception in a group of 41 healthy, regularly cycling women. Forearm ischemia was used to engage CPM, a form of endogenous inhibition. As a manipulation check, we verified from ratings that forearm ischemia evoked tonic painful sensations. And, as expected, this forearm ischemia pain inhibited NFR and pain ratings, indicating that descending brain-to-spinal cord mechanisms were engaged to modulate afferent nociception at the spinal level. Interestingly, pain ratings showed further inhibition in the 2 to 4 min post-ischemia, suggesting that it persisted longer for pain perception (i.e., analgesic after effects). By contrast, NFR inhibition returned to baseline values during post-ischemia. Although NFR and pain

![Fig. 2](image-url)

Fig. 2. The top graph (a) depicts CPM of subjective pain ratings across the mid-follicular and late-luteal phases. Pain was inhibited during ischemia and post-ischemia relative to pre-ischemia (baseline). Further, pain ratings were significantly lower during the late-luteal phase relative to the mid-follicular phase. The bottom graph (b) depicts CPM of the nociceptive flexion reflex (NFR) across the mid-follicular and late-luteal phases. NFR was inhibited during ischemia relative to pre-ischemia (baseline) and post-ischemia. Asterisk indicates that comparison was significant at \(p < 0.05\).
ratings often correlate [27], they can dissociate to reflect differential modulation of spinal vs. supraspinal processing [40, 49]. Thus, our observation that pain and NFR diverged during the post-ischemia phase may reflect that supraspinal circuits to inhibit pain were engaged during post-ischemia at the same time that descending brain-to-spinal cord circuits to inhibit spinal nociception were disengaged (Fig. 1). However, it could also be that pain ratings, but not NFR, were affected by habituation processes—although we typically find that pain sensitizes across the testing session whereas NFR tends to habituate [50]. Furthermore, report bias in pain ratings might have contributed to the divergence. Future research is needed to address these issues.

Contrary to our hypothesis, CPM inhibition did not differ across the mid-follicular and late-luteal phases. Therefore, findings from the current study extend those by Tousignant-Laflamme and Marchand [26]. Their study found that CPM inhibition of pain was similar during the menstrual (days 1–3) and mid-luteal (days 19–23) phases, but was stronger during the ovulatory phase. Our study demonstrated that CPM inhibition of pain ratings was not statistically different in the mid-follicular (days 5–8) and late-luteal (days 1–6 preceding menses) phases. Taken together, these studies suggest that CPM inhibition is similar throughout the majority of the menstrual cycle, but may be stronger during the ovulatory phase when several sex hormones surge (e.g., luteinizing hormone, follicular stimulating hormone, progesterone). Consistent with this interpretation, Tousignant-Laflamme and Marchand found a positive correlation between the level of progesterone and the degree of CPM inhibition, but only during the ovulation phase. These changes in endogenous pain inhibition may contribute to menstrual cycle-related changes in pain for women with and without clinical pain disorders [9–14].

Our study was the first to show that CPM inhibition of NFR did not vary across mid-follicular and late-luteal phases. This implies that descending brain-to-spinal cord modulation of spinal nociceptive processes may not contribute to the enhanced pain often observed during the late-luteal phase [9–14]. However, given that modulation of pain and NFR can diverge, it will be important for future studies to determine whether CPM inhibition of NFR is greater during ovulation, relative to other phases. A study is underway that addresses this issue.

We found that pain ratings of electrical stimuli were generally lower during the late-luteal phase compared to the mid-follicular phase throughout all stages of CPM testing. Given that clinical pain is typically enhanced during the late-luteal phase, this seems counterintuitive. While the reason for this interesting finding is unknown, it is consistent with some other studies that have found electric pain thresholds and tolerances to be higher (i.e., hypoalgesia) during the luteal phase, relative to the follicular phase [28].

Lower ratings of electric pain during the late-luteal phase are also consistent with other results published from the parent study [33]. We found that when suprathreshold electric stimulations were delivered during emotional pictures, emotion modulated pain ratings and NFR similarly in the mid-follicular and late-luteal phases. Specifically, in both phases, unpleasant pictures enhanced pain and NFR, whereas pleasant pictures inhibited pain and NFR. However, we also found that ratings of electric stimuli were lower during the late-luteal phase relative to the mid-follicular phase, regardless of the emotion evoked by the pictures. Taken together, these two studies suggest that pain in response to suprathreshold stimulations, but not modulation of pain in response to suprathreshold stimulations (i.e., CPM inhibition of pain, emotional modulation of pain), varies across the mid-follicular and late-luteal phases.

Limitations and Future Directions

Based on the recommendations of Sherman and LeResche [51], we took numerous steps to increase the methodological rigor of our investigation of menstrual cycle influences on CPM inhibition. Specifically, we recruited a relatively large sample size, verified ovulation through LH urine tests, confirmed menstrual cycle regularity via monitoring multiple cycles, and used powerful statistical procedures. Furthermore, our study is the first to evaluate CPM inhibition of NFR across the menstrual cycle. Despite these strengths, there are a few limitations worth noting.

First, we did not directly measure hormone levels. Both the mid-follicular and late-luteal phases are associated with low levels of estradiol, whereas progesterone levels are higher during the late-luteal phase. As a result, our findings suggest that progesterone may not impact CPM inhibition of pain and spinal nociception. However, without measuring intra- and interindividual variability in sex hormones, we are unable to directly test these relationships. Second, we assessed CPM inhibition only during the mid-follicular and late-luteal phases based on evidence that these two phases produce robust changes in pain perception [28]. However, given the findings of Tousignant-Laflamme and Marchard [26], it seems plausible that hormonal variation associated with other phases (e.g., ovulation) may contribute to changes in CPM inhibition of spinal nociception. Third, we took extra precautions to make sure that the late-luteal phase was not confounded by the ovulatory phase. Nonetheless, due to intra- and interindividual variability in menstrual cycle length, some women were not tested within the specific windows that we defined as the mid-follicular phase (N=4) and the late-luteal phase (N=8). However, when data were restricted to women who were tested during the specific windows, conclusions were the same, except that pain ratings were no longer lower during the late-luteal phase (p=0.059), probably due to lower power.
Importantly, our results regarding CPM inhibition of pain ratings and NFR were unchanged.

Fourth, we did not employ a nonpainful control condition for the ischemia paradigm. Some researchers have compared pain outcomes from the traditional paradigm (i.e., pre-ischemia, ischemia, post-ischemia) to pain outcomes obtained during nonpainful control procedures (pre-sham ischemia, sham ischemia, post-sham ischemia) [52]. That study design provides a means of controlling for pain modulatory effects unrelated to CPM (e.g., habituation, sensitization). Indeed, habituation may have contributed to the results for pain ratings in the present study, given that ratings continued to decrease during the post-ischemia phase. But, neither sensitization nor habituation can account for the NFR results. NFR was inhibited during ischemia, an effect that returned to baseline during post-ischemia. Therefore, we believe that our conclusions about CPM inhibition of NFR are valid.

Fifth, several of our conclusions are based on a failure to reject the null hypothesis. While caution is warranted in “accepting” the null hypothesis, confidence in our conclusions is bolstered by the fact that we used powerful statistical procedures that are able to detect small effect sizes. And finally, given research suggesting abnormalities in CPM inhibition among various clinical populations (i.e., fibromyalgia, chronic tension-type headache), our results may not generalize to individuals with chronic pain, or women with menstrual cycle-related disorders (i.e., PMDD, dysmenorrhea).

Conclusions

In sum, the present study suggests that differences in experimental pain that occur between the mid-follicular and luteal phases of the menstrual cycle are not due to differences in brain-to-spinal cord modulation of nociception at the spinal level. Future studies are needed to (1) study CPM inhibition of NFR during the ovulation phase, (2) replicate findings in a clinical population (e.g., PMDD, fibromyalgia), and (3) assess the relationships between sex hormone levels and CPM efficacy across multiple phases of the menstrual cycle.

Acknowledgments The authors would like to thank Mary C. Chandler, Kara L. Kerr, and Ashley L. Vincent for their assistance in data collection and data processing for this study. This work was funded by a Future Leaders in Pain Research Grant awarded to Jamie L. Rhudy, Ph.D. from the American Pain Society.

Conflict of Interest Statement The authors have no conflicts of interest to report.

References


