Acetaminophen does not affect 24-h body temperature or sleep in the luteal phase of the menstrual cycle

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Baker, Fiona C., Helen S. Driver, Janice Paiker, Geoffrey G. Rogers, and Duncan Mitchell. Acetaminophen does not affect 24-h body temperature or sleep in the luteal phase of the menstrual cycle. J Appl Physiol 92: 1684–1691, 2002. First published December 7, 2001; 10.1152/japplphysiol.00919.2001.—Body temperature and sleep change in association with increased progesterone in the luteal phase of the menstrual cycle in young women. The mechanism by which progesterone raises body temperature is not known but may involve prostaglandins, inducing a thermoregulatory adjustment similar to that of fever. Prostaglandins also are involved in sleep regulation and potentially could mediate changes in sleep during the menstrual cycle. We investigated the possible role of central prostaglandins in mediating menstrual-associated 24-h temperature and sleep changes by inhibiting prostaglandin synthesis with a therapeutic dose of the centrally acting cyclooxygenase inhibitor acetaminophen in the luteal and follicular phases of the menstrual cycle in young women. Body temperature was raised, and nocturnal amplitude was blunted, in the luteal phase compared with the follicular phase. Acetaminophen had no effect on the body temperature profile in either menstrual cycle phase. Prostaglandins, therefore, are unlikely to mediate the upward shift of body temperature in the luteal phase. Sleep changed during the menstrual cycle: on the placebo night in the luteal phase the women had less rapid eye movement sleep and more slow-wave sleep than in the follicular phase. Acetaminophen did not alter sleep architecture or subjective sleep quality. Prostaglandin inhibition with acetaminophen, therefore, had no effect on the increase in body temperature or on sleep in the midluteal phase of the menstrual cycle in young women, making it unlikely that central prostaglandin synthesis underlies these luteal events.

Acetaminophen; progesterone; rapid eye movement sleep; slow-wave sleep

Women with ovulatory menstrual cycles show an increase in body temperature (of ~0.3–0.4°C) in the luteal phase, compared with the preovulatory follicular phase. The circadian rhythm of temperature also may be altered with menstrual cycle phase: circadian amplitude may be blunted (8, 11, 25, 27, 35), although not always (4), and phase may be delayed, with the minimum body temperature occurring later (8), in the luteal phase compared with the follicular phase. The luteal phase elevation in body temperature is mediated by progesterone. Body temperature rises rapidly in response to progesterone administration in rabbits (34) and in young men (38) and increases ~24 h after a detectable increase in progesterone plasma concentration in women (24). The mechanism of thermogenic action of progesterone is unknown, although it is thought to be central rather than peripheral (7). The rise in body temperature in the luteal phase and the apparently normal thermoregulation around this elevated body temperature are reminiscent of the thermoregulatory changes associated with fever (26). Because the change in thermoregulatory set point in fever is mediated by cyclooxygenase (COX), prostaglandins or other prostanoids might also underlie the thermoregulatory effects of progesterone in the menstrual cycle. Indeed, blood prostaglandin concentrations are increased in the midluteal phase (15).

Thermoregulatory changes are not the only putative progesterone-mediated changes in physiological rhythms in the menstrual cycle. The menstrual cycle hormones influence sleep (see Ref. 12 for review). Rapid eye movement (REM) sleep has been reported to be reduced in the luteal phase, (2, 13), although not always (4), and stage 2 non-REM sleep may increase (13), but again not always (2, 28). These changes in sleep have also been attributed to progesterone (13), and, as for body temperature, could involve prostaglandins. Prostaglandins influence sleep: PGD2 promotes sleep, whereas PGE2 induces wakefulness in animal models (19). Few studies have investigated the involvement of prostaglandins in sleep-wake regulation in healthy humans, and these studies rely on inhibiting COX activity. Findings are variable. COX inhibitors may suppress slow-wave sleep (SWS) and increase stage 2 sleep (22), increase time spent awake and reduce sleep efficiency without affecting SWS (32), or have no effect on

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sleep, at least in young women in the follicular phase and in young men (32).

COX inhibitors have been used to investigate the interaction between progesterone and heat stress in awake women, and results indicate that prostaglandins are not involved (7, 9). In both of these studies, body temperature was only measured for a short daytime period, mostly in women who were taking synthetic steroids (7, 9). But synthetic steroid hormones, such as those contained in oral contraceptives, influence body temperature and sleep differently from endogenous progesterone and estrogen (3). As far as we are aware, no previous study has investigated the involvement of prostaglandins in the upward shift of body temperature over 24 h and sleep in the natural luteal phase.

Members of the COX family are found in a variety of tissues (14). However, if prostaglandins are involved in mediating progesterone-induced effects on temperature and sleep in the luteal phase, then the candidate prostaglandins are likely to be synthesized by COX in the brain. A centrally mediated effect is proposed, given the neurological basis of sleep and because the thermogenic effects of progesterone are likely central (7). Also, the change in set point during fever, of which the luteal temperatures are reminiscent, occurs through actions of prostaglandin in the brain (29). The appropriate COX inhibitor to use in this case, therefore, is one that acts preferentially on brain COX, such as acetylsalicylic. Acetylsalicylic exerts its antipyretic action in the central nervous system, probably by inhibiting a specific isoform of COX, which may be a variant of COX-2 or a unique isoform provisionally named COX-3 (6, 45).

To investigate the possible involvement of prostaglandins in sleep and 24-h body temperature in general, as well as in luteal phenomena, we administered acetylsalicylic in the follicular and luteal phases of the menstrual cycle in the same women. We included in our subject group women who suffered from primary dysmenorrhea. Previously, we found that such women had a higher nocturnal body temperature than women without dysmenorrhea (2), which we postulated might also be mediated by prostaglandins.

METHODS

Subjects. Thirteen healthy young women without any menstrual-associated complaints (21 ± 3 yr) and 10 women with primary dysmenorrhea (23 ± 4 yr), with onset soon after menarche, were recruited from a university student population and consented to participate in our study. Ethical clearance was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand (clearance no. M990203), which adheres to the principles of the Declaration of Helsinki. All of the women completed questionnaires and were interviewed to ensure that they had regular sleep-wake schedules, were nonsmokers, and showed no indication of sleep or medical disorders. All of the volunteers were of normal psychological status, as assessed with the 30-item version of the General Health Questionnaire, which correlates well with psychiatric interview (18). The women were asked specifically about any mood changes that occurred during their menstrual cycles. None reported evidence of premenstrual syndrome (31). The dysmenorrheic women were classified as having mild-to-moderate dysmenorrhea (1). The absence of any pathology was confirmed by a gynecological examination.

Experimental procedure. For a month after entering the study, the women completed a calendar of premenstrual experiences (31), which confirmed that none suffered from premenstrual syndrome. They measured their oral temperature every morning before getting out of bed using a digital thermometer (Soar M.E., Nagoya, Japan) and used a commercially available self-test kit, which detects the presence of luteinizing hormone (LH) in urine (ClearPlan One Step, Unipath, Bedford, UK), to confirm ovulation. Only women who had predictable and ovulatory menstrual cycles, as assessed by a biphasic temperature rhythm and the midcycle presence of LH, were accepted for the recording phase of the study. Twelve of the thirteen women without any menstrual-related disorders and all ten dysmenorrheic women fulfilled these criteria and participated in the study during the summer and autumn months.

All of the subjects were requested to maintain their customary weekday bedtime schedules, even on the weekend, for at least 1 wk before a scheduled study night. On study nights, the women maintained their habitual schedules but slept in the controlled environment of our laboratory. Each woman spent at least 5 nights in the laboratory: 1 adaptation night and 2 recording nights in both the midfollicular phase (7–10 nights after the onset of menstrual flow) and the midluteal phase (5–8 nights after the LH surge). The 2 recording nights in each phase were separated by 1 night spent at home. The adaptation night, held 1 or 2 nights before the first recording night, allowed the subjects to familiarize themselves with the environment and recording equipment. Seven of the control women and seven of the dysmenorrheic women had their first recording night in the follicular phase. Four of the women returned to the sleep laboratory for a repeat recording, owing to incomplete data collection or transient illness.

Medication. On each of the recording days, the women were randomly given either acetaminophen (= paracetamol, 650 mg/capsule, Tylenol Extended Relief Caplets, Janssen-Cilag Pharmaceuticals, Johannesburg, South Africa) or placebo (potato starch in an identical capsule), according to a double-blind, crossover design within one menstrual cycle. Each woman took a total of six capsules within each 24 h recording period: two capsules between 5 and 8 h before bedtime, two capsules at lights-out, and two capsules on awakening. The total amount of acetaminophen taken over 24 h, therefore, was 3,900 mg, the maximum adult dose registered for treatment of fever. The women were not taking any medication other than that required for the study.

Data acquisition and analysis. Standard polysomnographic electroencephalographic (EEG), electrooculographic, and electromyographic recordings were made on a digital EEG (Medelec DG 20, Vickers Medical, Surrey, UK) at a virtual recording speed of 15 mm/s and with a sampling rate of 240 Hz. Low- (0.5 Hz) and high-frequency (30 Hz) filters were applied to the EEG data before analysis. Twenty-second epochs were scored according to modified standard criteria.
Rectal temperatures were recorded every minute for at least 60 h. Recordings started at least 4 h before lights-out on the first day and included both recording nights, the night spent at home, and the intervening day in each menstrual phase. Temperature was recorded using indwelling rectal thermistors connected to miniature temperature data loggers (Stowaway XTI, Onset Computer, Pocasset, MA), custom modified to have a narrow temperature range (34–46°C) and high resolution (0.04°C). The thermistors were encased in a polythene sheath and inserted into the rectum to a depth of ∼100 mm. Subjects recorded the times when they removed the probe for bathing or using the toilet, and the missing temperatures were calculated by linear interpolation. Ambient dry-bulb temperature in the laboratory was recorded every 30 min by a thermocouple array connected to a fixed data logger (MC Systems, Cape Town, South Africa). Ambient temperature was maintained between 21 and 23°C throughout the study. All thermistors and thermocouples were calibrated by water immersion against a quartz thermometer (Quat 100, Heraeus, Hanau, Germany) to an accuracy of at least 0.1°C. The miniature data loggers maintain accuracy even in the face of changing environmental temperatures (17).

Rectal temperature data were smoothed by a 15-min moving average of the 1-min recordings. We then calculated mean 24-h and minimum temperatures. The time of the minimum temperature for each individual was determined from visual inspection of the smoothed temperature curves. We also measured the extent of the nocturnal drop in body temperature for each subject using the thermal response index, an index used frequently by thermal physiologists. In our case, the thermal response index was the time integral (°C/h), over 410 min, of the change in rectal temperature vs. time from the temperature recorded 10 min after lights-out (i.e., the area between the actual curve of rectal temperature vs. time and a horizontal line drawn through the temperature recorded 10 min after lights-out). We also calculated average temperatures for designated nighttime (2100–0859) and daytime (0900–2059) 12-h periods, within each 24-h recording period, for each subject. We then calculated mean differences in temperature between the luteal and follicular phases for each condition (placebo or acetaminophen) separately for day and nighttime periods.

Before going to bed, the women completed a questionnaire describing the events of that day and indicated their evening anxiety on a 100-mm visual analog scale (VAS), anchored from terribly agitated to utterly calm and peaceful. After each recording night, the subjects assessed the preceding night’s sleep quality on a 100-mm VAS with anchor points of worst possible and best ever sleep. Morning vigilance was rated on a similar VAS, anchored from feeling awfully sleepy and lackluster to feeling marvelously alert and energetic. The subjective VAS measurements (in mm) were normalized before statistical analysis through the arcsine square-root transform.

A 5-ml blood sample was taken from the women between 0700 and 0800, after 1 of the recording nights in each phase. The serum was frozen for later determination of estradiol, progesterone, and prolactin, using automated chemiluminescent immunoassays (Bayer Diagnostics, Tarrytown, NY), which were performed on one blood sample from each individual for each hormone assay. The mean within-assay variation was 7.2% in the estradiol assay, 6.6% in the progesterone assay, and 2.8% in the prolactin assay.

Statistical analysis. We evaluated sleep over the first 7 h of the recording nights because it was the shortest period for which all subjects were in bed. We excluded three of the women without menstrual complaints and one of the dysmenorrheic women from analysis because they did not show an increase in serum progesterone or body temperature in the latter period of their cycles; therefore, we could not be sure that they had ovulated. We also excluded one of the women without complaints and one of the dysmenorrheic women because their acetaminophen use was greater than 2 SD from the mean on their acetaminophen and placebo nights, respectively, in the luteal phase.

We investigated differences in temperature and differences in subjective and objective sleep measures using a two-way repeated-measures multivariate ANOVA (MANOVA) at a 95% confidence interval, according to study group, menstrual phase, and drug. We failed to detect any significant differences between the women without complaints and those with dysmenorrhea in any of the variables assessed; therefore, we subsequently grouped the women together and performed a repeated-measures MANOVA, with factors of menstrual phase and drug, for each variable. When appropriate, the Student Newman-Keuls (SNK) test was used to identify the origins of any differences. We used paired t-tests to compare hormone concentrations in the follicular and luteal phases. Data from 16 women (age: 22 ± 4 yr; mass: 60.1 ± 8.4 kg; height: 1.65 ± 0.05 m; body mass index: 22.1 ± 2.8 kg/m²; menstrual cycle length: 28 ± 2 days) were used in the final sleep analysis. One of these women was excluded from the temperature analysis because of frequent slippage of the rectal probe. Sleep and temperature data for eight of the women (all controls) on their placebo nights only have previously been reported (3).

RESULTS

Hormones. The women had significantly higher plasma progesterone concentrations [paired t-test: t(15) = 12.4, P < 0.0001] in the luteal phase (35 ± 11 nmol/l) than in the follicular phase (2 ± 1 nmol/l). Plasma estrogen concentrations were increased t(15) = 4.4, P = 0.0005] in the luteal phase (530 ± 180 pmol/l) compared with the follicular phase (260 ± 180 pmol/l). Prolactin concentrations were the same in the luteal phase (19 ± 8 μg/l) and the follicular phase (18 ± 10 μg/l). All hormone concentrations were within the normal ranges for follicular and luteal phases (42).

Body temperature. Figure 1 shows the average smoothed rectal temperature curves for 4 h before lights-out and 20 h thereafter for the women taking either placebo or acetaminophen in each menstrual phase. Rectal temperature started dropping before bedtime, associated with the declining phase of body temperature and reduced activity of the women, and
continued to drop sharply after lights-out, as the women assumed a recumbent position and fell asleep. Body temperature increased markedly after lights-on. As expected, the women had significantly raised body temperatures, with higher mean 24-h, lights-out, 7-h in-bed, and minimum temperatures in the luteal phase compared with the follicular phase (Table 1). The difference in luteal-follicular phase body temperatures during the 12-h nighttime period (placebo: 0.40 ± 0.1°C, acetaminophen: 0.35 ± 0.1°C) was larger (MANOVA phase effect: $F_{1,14} = 16, P = 0.001$) than during the 12-h daytime period (placebo: 0.25 ± 0.2°C, acetaminophen: 0.26 ± 0.2°C), indicating that the nocturnal decline in body temperature during the luteal phase was dampened. Also, the in-bed thermal response index was smaller, implying less of a drop in body temperature, in the luteal phase than in the follicular phase (Table 1). The time at which the minimum body temperature occurred was not significantly affected by menstrual cycle phase (Table 1). Acetaminophen had no effect on any of the body temperature variables measured in each menstrual phase (Table 1). The apparent difference in minimum body temperatures between the placebo and acetaminophen conditions (Fig. 1) is an artifact of plotting a mean temperature curve for several individuals, regardless of the timing of their minimum temperatures.

**Subjective assessments.** Before going to bed, subjective assessments of anxiety were the same (phase: $F_{1,15} = 0.1, P > 0.5$; drug: $F_{1,15} = 0.3, P > 0.4$) for the placebo (71 ± 27 mm) and acetaminophen (73 ± 27 mm) conditions in the follicular phase as they were in the luteal phase (placebo: 73 ± 21 mm; acetaminophen: 67 ± 24 mm). The women also reported a similar sleep quality (drug: $F_{1,15} = 0.6, P > 0.6$) for the placebo (64 ± 22 mm) and acetaminophen (71 ± 22 mm) nights in the follicular phase, which did not differ (phase: $F_{1,15} = 0.4, P > 0.7$) from that in the luteal phase (placebo: 71 ± 19 mm; acetaminophen: 68 ± 24 mm). Finally, the women reported relatively high morning vigilance levels (63 ± 21 mm) when taking placebo and when taking acetaminophen (68 ± 18 mm) in the follicular phase and similar levels (phase: $F_{1,15} = 0.01, P > 0.9$; drug: $F_{1,15} = 1.1, P > 0.3$) in the luteal phase (placebo: 64 ± 18 mm; acetaminophen: 66 ± 20 mm).

**Sleep composition.** Table 2 shows selected sleep variables for the first 7 h after lights-out. The range of times over which the women elected to go to bed and woke up differed by <90 min, and the group means by <10 min between phases of the experiment. The women had significantly less REM sleep in the luteal phase than in the follicular phase, regardless of whether they were taking acetaminophen or placebo (Table 2). On the placebo night in the luteal phase, SWS time was longer, and combined time spent awake, moving, and in stage 1 sleep was shorter, than on the placebo night in the follicular phase (Table 2).

Sleep in the follicular phase was unaffected by acetaminophen (Table 2). In the luteal phase, latency to stage 3 sleep was significantly longer, but only by 2 min, when the women took acetaminophen compared with placebo (Table 2). Time spent in the various sleep stages in the luteal phase was not significantly affected

Table 1. Rectal temperature variables and statistical comparisons of 15 young women when they took either acetaminophen or placebo in the midfollicular and midluteal phases of their menstrual cycle.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Follicular Phase</th>
<th>Luteal Phase</th>
<th>Statistical Comparison, MANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lights-out temperature, °C</td>
<td>Placebo</td>
<td>Acetaminophen</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>37.0 ± 0.2</td>
<td>37.0 ± 0.2</td>
<td>37.4 ± 0.3°</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug: $F_{1,14} = 0.4, ns</td>
</tr>
<tr>
<td>Minimum temperature, °C</td>
<td>36.4 ± 0.2</td>
<td>36.4 ± 0.2</td>
<td>36.9 ± 0.1°</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug: $F_{1,14} = 0.04, ns</td>
</tr>
<tr>
<td>Mean 7-h in-bed temperature, °C</td>
<td>36.6 ± 0.1</td>
<td>36.7 ± 0.2</td>
<td>37.1 ± 0.1°</td>
</tr>
<tr>
<td>Mean 24-h temperature, °C</td>
<td>37.1 ± 0.1</td>
<td>37.1 ± 0.1</td>
<td>37.4 ± 0.1°</td>
</tr>
<tr>
<td>In-bed thermal response index, °C/h</td>
<td>−1.6 ± 1.5</td>
<td>−1.7 ± 1.2</td>
<td>−1.3 ± 1.6°</td>
</tr>
<tr>
<td>Time of minimum temperature</td>
<td>01:13 ± 116 min</td>
<td>01:47 ± 129 min</td>
<td>02:33 ± 139 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phase: $F_{1,14} = 0.6, ns</td>
</tr>
</tbody>
</table>

Values are means ± SD. Temperature data from 1 woman was excluded from analysis because of frequent slippage of the rectal probe. MANOVA, multivariate ANOVA; ns, not significant. *Significantly different from follicular phase.
Table 2. Selected sleep variables during the first 7 h of sleep after lights-out and statistical comparisons for 16 young women when they took either acetaminophen or placebo in the midfollicular and midluteal phases of their menstrual cycles.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Follicular Phase</th>
<th>Luteal Phase</th>
<th>Statistical Comparison, MANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Acetaminophen</td>
<td>Placebo</td>
</tr>
<tr>
<td>Time of lights-out</td>
<td>22:53 ± 11 min</td>
<td>22:59 ± 11 min</td>
<td>22:58 ± 11 min</td>
</tr>
<tr>
<td>Time of lights-on</td>
<td>06:22 ± 21 min</td>
<td>06:21 ± 21 min</td>
<td>06:30 ± 21 min</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>39 ± 8 min</td>
<td>397 ± 7 min</td>
<td>397 ± 10 min</td>
</tr>
<tr>
<td>Sleep onset latency, min</td>
<td>13 ± 7 min</td>
<td>12 ± 6 min</td>
<td>12 ± 8 min</td>
</tr>
<tr>
<td>Latency to stage 3 sleep, min</td>
<td>10 ± 3 min</td>
<td>10 ± 3 min</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>Latency to REM sleep, min</td>
<td>62 ± 14 min</td>
<td>65 ± 17 min</td>
<td>62 ± 11</td>
</tr>
<tr>
<td>Stage 2 sleep, %</td>
<td>41 ± 3 %</td>
<td>39 ± 4 %</td>
<td>40 ± 5</td>
</tr>
<tr>
<td>Slow-wave sleep, %</td>
<td>24 ± 3 %</td>
<td>26 ± 5 %</td>
<td>28 ± 5%§</td>
</tr>
<tr>
<td>REM sleep, %</td>
<td>22 ± 2 %</td>
<td>23 ± 2 %</td>
<td>20 ± 3†</td>
</tr>
<tr>
<td>Awake, movement, and stage 1 sleep, %</td>
<td>11 ± 2 %</td>
<td>9 ± 2 %</td>
<td>9 ± 3%§</td>
</tr>
</tbody>
</table>

Values are means ± SD. REM, rapid eye movement. *Significantly different from placebo; †significantly different from follicular phase; §significantly different from follicular phase (placebo); Student Newman-Keuls, P < 0.05; ‡significantly different from follicular phase (acetaminophen), Student Newman-Keuls, P = 0.007.
analyzed in two groups because we previously found that dysmenorrheic women had higher nocturnal body temperatures and slightly less REM sleep than did asymptomatic women (2). In our present study, however, we found no significant differences in body temperature or sleep between the two groups of women. Our sample size of only eight women with dysmenorrhea (or seven for temperature analysis) in this study may have been too small to replicate the small differences found previously. Although we did not find differences in sleep and temperature between women with and without dysmenorrhea, this does not confound our conclusion concerning brain prostaglandin synthesis.

Consistent with the findings of others (8, 11, 25, 27, 35), body temperature was raised over 24 h and exhibited a smaller drop during the night in the luteal phase compared with the follicular phase. In an earlier study, our laboratory did not find a significant difference in the nocturnal temperature drop in the luteal phase compared with the follicular phase in eight young women (4). Variation that exists among individuals in body temperature profiles and the menstrual cycle may necessitate larger sample sizes being investigated to find an effect. Both the increased 24-h temperature and the nocturnal blunting in the luteal phase are conventionally attributed to increased progesterone concentrations. Body temperature during fever is also shifted upward and apparently regulated around the elevated level (26). Thus we postulated that the thermal events of the luteal phase may depend on COX activity in the brain, as fever does (29). However, our results do not support this assumption. Our findings support those of others who have shown that the body temperature-raising effect of progesterone is unlikely to involve prostaglandins (7, 9). Additionally, we have shown that the nocturnal blunting of body temperature in the luteal phase also is unlikely to be mediated by prostaglandins. Progesterone may act through a pathway independent of prostaglandins to induce an upward shift in the thermoregulatory set point in the luteal phase. Prostaglandin-independent pathways that induce fever have been identified, involving factors such as corticotropin-releasing factor, endothelin-1, interleukin-8, or the carbon monoxide-heme pathway (43). Alternatively, progesterone may act directly on thermoregulatory neurons in the preoptic anterior hypothalamus. Indeed, progesterone rapidly increases the firing rate of cold-sensitive neurons and decreases the firing rate of warm-sensitive neurons (34), with a consequent rise in body temperature.

In the absence of progesterone, in women in the follicular phase and in men, a therapeutic dose of either aspirin or ibuprofen has been reported to attenuate the circadian decline in body temperature (33). The authors attributed this effect to the inhibition of COX in the pineal gland with a consequent suppression of melatonin secretion and its hypothermic effect (33). We did not find any change in the circadian profile of body temperature in the follicular phase after acetaminophen treatment, which ought to inhibit pineal COX. The study protocol of Murphy et al. (33) differed from ours in that body temperature was measured at the tympanic membrane, once every 15 min, while the subjects were seated and kept awake for the 4-h nighttime recording period. The amplitude of the nocturnal decline in body temperature is reduced in sleep-deprived subjects (5) and may have been influenced further because the subjects were seated rather than recumbent. We measured temperature continuously in the rectum, which better reflects core body temperature than does the tympanic membrane (16), and our subjects were allowed to sleep normally.

Acetaminophen failed to influence not only body temperature but also sleep architecture. It is unlikely, therefore, that any changes in sleep architecture in the luteal phase result from central COX activity. Our finding, that a therapeutic dose of acetaminophen did not greatly alter sleep in the young women in our study, supports that of Murphy et al. (32) in young women in the follicular phase and in young men. COX inhibitors that have both a peripheral and a central action, however, do alter sleep; aspirin and ibuprofen increase wakefulness and disrupt sleep (32). It remains to be investigated whether a COX inhibitor with peripheral activity influences menstrual-associated changes in sleep.

Drug dosage regimen may affect the extent of the influence on sleep of COX inhibitors. Horne et al. (22) found that aspirin, given over 3 days, decreased SWS and increased stage 2 sleep, without affecting time spent awake. These changes in sleep found by Horne et al. are reminiscent of the small changes in our women in the luteal phase after acetaminophen administration.

The small decrease in REM sleep that we found in the luteal phase compared with the follicular phase is similar to our previous findings (2) and to the trend reported by Driver et al. (13). Progesterone may mediate the decrease in REM sleep in the luteal phase: young men showed a significant reduction in REM sleep after synthetic progesterone administration (46). The decrease in REM sleep also could be a consequence of the raised body temperature in the luteal phase. Because thermoregulatory responses are disrupted during REM sleep (see Ref. 20 for review), REM sleep may be inhibited in the presence of elevated body temperatures. We have not previously found an increase in SWS in the luteal phase compared with the follicular phase (2, 4, 13), as we did in this study, but others have done so (21, 41). Progesterone and its metabolites enhance the effects of GABA (40) and may enhance SWS. Schulz et al. (39) found an increase in amplitude in the delta frequency range of the EEG in young men after administration of pregnanolone, a neuroactive metabolite of progesterone. Moldofsky et al. (30), however, found a decrease in SWS in the luteal phase compared with the follicular phase that correlated with plasma progesterone concentrations. Different study protocols, small sample sizes, and different sampling times during the menstrual cycle may mask small SWS effects in the luteal phase. It is clear, too,
that the endogenous increase in body temperature in the luteal phase does not have the same consequences as experimentally increasing body temperature before bedtime, which consistently induces an increase in SWS (23).

In conclusion, we found that a therapeutic dose of acetaminophen had no effect on the increase in body temperature and little effect on the changes in sleep architecture in the luteal phase of young women, making it unlikely that central COX activity underlies the luteal events. If the events are caused by the increased concentration of progesterone during the luteal phase, then progesterone may act directly on the brain or via mediators other than centrally synthesized prostaglandins.

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