Estrogen modifies the temperature effects of progesterone

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ESTACHENFELD, NINA S., CELSO SILVA, AND DAVID L. KEEFE. Estrogen modifies the temperature effects of progesterone. J Appl Physiol 88: 1643–1649, 2000.—To test the hypothesis that progestin-mediated increases in resting core temperature and the core temperature threshold for sweating onset are counteracted by estrogen, we studied eight women (24 ± 2 yr) at 27°C rest, during 20 min of passive heating (35°C), and during 40 min of exercise at 35°C. Subjects were tested four times, during the early follicular and midluteal menstrual phases, after 4 wk of combined estradiol-norethindrone (progestin) oral contraceptive administration (OC E + P), and after 4 wk of progestin-only oral contraceptive administration (OC P). The order of the OC P and OC E + P were randomized. Baseline esophageal temperature (T es) at 27°C was higher (P < 0.05) in the luteal phase (37.08 ± 0.21°C) and in OC P (37.60 ± 0.31°C) but not during OC E + P (37.04 ± 0.23°C) compared with the follicular phase (36.66 ± 0.21°C). T es remained above follicular phase levels throughout passive heating and exercise during OC P, whereas T es in the luteal phase was greater than in the follicular phase throughout exercise (P < 0.05). The T es threshold for sweating was also greater in the luteal phase (38.02 ± 0.28°C) and OC P (38.07 ± 0.17°C) compared with the follicular phase (37.32 ± 0.11°C) and OC E + P (37.46 ± 0.18°C). Progestin administration raised the T es threshold for sweating during OC P, but this effect was not present when estrogen was administered with progestin, suggesting that estrogen modifies progestin-related changes in temperature regulation. These data are also consistent with previous findings that estrogen lowers the thermoregulatory operating point.

progestin; thermoregulation; menstrual cycle; exercise

RESTING CORE BODY TEMPERATURE (18, 31) and the temperature thresholds for sweating (31) and vasodilation (17, 31) during exercise are greater during the midluteal phase and in women taking oral contraceptives (OC) (7) compared with the follicular phase of the menstrual cycle. The core temperature increases are concomitant with the progesterone peak in the midluteal phase (18), do not occur in anovulatory cycles (26), and consistently occur with progesterone administration in animals (24). In contrast, the regulated body temperature in women is at its lowest during the late follicular phase coincident with the cyclic estrogen surges (33), and estrogen treatment in postmenopausal women reduces resting body temperature and core temperature thresholds for sweating and vasodilation during exercise (34). Taken together, the available evidence suggests that high blood progesterone levels are responsible for a greater core temperature and that estrogen alone reduces regulated body temperature in women.

The mechanism by which estrogen and progesterone affect the regulated body temperature has not been established in humans. Sex steroids most likely impact thermoregulation through action in the brain to change the regulated hypothalamic temperature. Studies in animals have shown that estrogen and progesterone can act directly on specific sex steroid-binding neurons in the preoptic/anterior hypothalamus (21, 27). Conversely, estrogen and progesterone may also act on the thermoregulatory system indirectly through cytokines (4) or systems that regulate fluid balance (30). Finally, estrogen could exert its effect on temperature regulation through locally mediated peripheral effects, such as on blood vessels to relax the vascular smooth muscle and to inhibit vasoconstrictor tone (16, 20), although chronic estrogen administration, with and without progesterone, does not alter resting or maximal skin blood flow in postmenopausal women (3).

The synthetic progestins and estrogens in oral contraceptives could potentially impact the thermoregulatory system in the same manner as the endogenous hormones. Based on thermoregulatory changes in the midfollicular and midluteal phases of the menstrual cycle, we would predict that the progestin component of the pill would override the estrogen component to increase the hypothalamic set-point temperature and, consequently, the regulated body temperature. In support of this hypothesis, chronic combined (estrogen + progesterone) OC administration induced an upward shift in regulated body temperature during rest (22°C) (25), passive heating (6, 8), and exercise (14, 25), and the progestin treatment eliminated the temperature-lowering effect of estrogen during combined hormone therapy in postmenopausal women (2).

Despite the progress in characterizing the effects of estrogen and progesterone on temperature regulation, much remains to be elucidated. For example, the effects of progesterone administration alone on resting and
exercise core temperatures in young women have not been determined nor has it been established to what extent estrogen modifies the progestosterone effects. Estrogen can act on progestosterone receptors in the reproductive system (28), so it may have similar effects on the preoptic area and anterior hypothalamus to affect temperature regulation. Most previous investigators studying oral contraceptive effects on the regulated body temperature in young women report chronic effects of therapy in a cross-sectional design (25) or in a within-subject design that uses the subjects’ week off from the pill as a control (6–8). These comparisons are limited because they do not allow for within-subject analysis in the first instance and do not account for the variable tissue washout rates of synthetic progestins and estrogens in oral contraceptives in the second instance.

To determine progestosterone effects on the body temperature regulation system, and the potential modifying influence of estrogen on those effects, we administered progestin (norethindrone)-only (OC P) and combined (ethenyl estradiol and norethindrone; OC E + P) oral contraceptives to young women in a randomized, crossover design. We then evaluated how each treatment affected the regulated body temperature by assessing resting core temperature and thermal responses to passive heating (35°C) and exercise in the heat (35°C). We hypothesized that progestin administration would increase resting core temperature and increase the core temperature threshold for onset of sweating, and these responses would be counteracted by estrogen administration with progesterone during combined oral contraceptive administration. Plasma volume adjustments to both OC treatments were also determined to assess the contribution of changes in blood volume to changes in temperature.

METHODS

Study Design

Subjects were nine healthy, nonsmoking women (age 24 ± 2 yr, range 19–28 yr) with no contraindications to oral contraceptive use. All subjects were interviewed about their medical history, underwent medical and gynecological examinations, and provided written confirmation of a negative Papanicolaou smear within 1 yr of being admitted to the study. During the month (early follicular phase) preceding the first heat stress experiment, resting plasma volume was determined with Evans blue dye dilution (see Blood Volume Measurements, Komaki, Japan), heart rate, and cardiac stroke volume (see Measurements) were recorded at the end of the 45-min control period. At the end of the control period, a blood sample (12 ml) was drawn. Hydration state was assessed from the specific gravity of the baseline urine sample (mean = 1.002 ± 0.001).

After the control measurements, the chamber temperature was increased to 35°C and the subject sat quietly for 20 min of passive heating. Measurements were made of arterial blood pressure every 10 min, of cardiac output at 15 min, and of T es and mean T sk continuously. At the end of the passive heating, another blood sample (12 ml) was drawn. Immediately after passive heating, the subjects exercised on a recumbent bicycle at 60% of their individual VO2peak for 40 min. The subjects exercised with a fan positioned directly in front of the bike, with a fan speed of 1.6 m/s to promote continuous evaporative sweating (1). Blood pressure was measured every 10 min, T es and mean T sk were monitored continuously, and cardiac output estimates were obtained at 15 and 35 min during exercise. Sweating rate was also determined continuously throughout exercise. Blood samples were drawn at 10, 20, and 40 min of exercise.

Measurements

Body core temperature (T es) was measured continuously from an esophageal thermocouple at the level of the left atrium. T sk was measured on the forehead, chest, upper arm, lateral flank, thigh, and calf. T es and T sk were collected at a rate of 5 data points per second. Data were stored in a
computer through an analog-to-digital converter system (ACRO 931, Daisylab, National Instruments, Austin, TX) as a mean value of every 30 s. Mean \( T_{sk} \) was calculated from the following equation, which takes into consideration surface area (23) and the thermosensitivity of each skin area (23)

\[
T_{sk} = 0.10\, T_{ch} + 0.21\, T_{fh} + 0.28\, T_{ab} + 0.18\, T_{ua} + 0.15\, T_{th} + 0.18\, T_{ca}
\]

where subscripts refer to mean skin (sk), chest (ch), forehead (fh), abdomen (ab), upper arm (ua), thigh (th), and calf (ca) values. An automatic dew-point sensor enclosed in a ventilated Plexiglas capsule was placed on the forearm and secured with surgical glue to determine sweating rate (12).

Cardiac stroke volume was measured noninvasively by impedance cardiography (Minnesota Impedance Cardiograph, Model 304B), with two silver tape electrodes placed around the neck and secured with surgical glue to determine sweating rate (12). Cardiac stroke volume was measured noninvasively by impedance cardiography (Minnesota Impedance Cardiograph, Model 304B), with two silver tape electrodes placed around the neck and secured with surgical glue to determine sweating rate (12).

Blood and Urine Analysis

From each blood sample, an aliquot (1 ml) was removed for immediate assessment of Hct, [Hb], and [TP] in triplicate by microhematocrit, cyanomethemoglobin, and refractometry respectively. A second aliquot was transferred to a heparinized tube, and a third aliquot was placed into a tube without anticoagulant for the determination of serum concentrations of sodium and potassium. The control blood samples were also analyzed for 17β-estradiol (P\textsubscript{E2}) and progesterone (P\textsubscript{P4}) concentrations.

Changes in plasma volume (PV) were estimated from changes in Hct and [Hb] from the control (preexercise) sample according to the equation

\[
\%\Delta PV = 100(\frac{[Hb]_b}{[Hb]_a})\frac{[Hct]_a - [Hct]_b}{[Hct]_a - [Hct]_b} - 100
\]

in which subscripts a and b denote measurements at time a and control, respectively. We used this equation to calculate both changes from baseline during exercise within a given experimental day as well as changes between each experimental day vs. the follicular phase. This equation has been demonstrated to be reliable and valid under stressful conditions (13), and red cell mass does not change over the menstrual cycle (10).

Electrolyte losses in urine were calculated by multiplying the volume of water loss in each fluid by the concentration of the electrolyte within the fluid. Total body sweat loss was calculated from the change in body weight during exercise.

Statistics

We used the 30-s averages to determine individual \( T_{es} \) thresholds for the onset of sweating. Each subject's sweating rate was plotted as a function of \( T_{es} \) during exercise, and the \( T_{es} \) threshold for sweating (i.e., the \( T_{es} \) above which the effector response is greater than that of baseline) was determined by two independent investigators. The average estimate was used for analysis, and the estimates had an interrater reliability of 0.95. For other analyses, before statistical treatment, the independent variable (time) was partitioned into 5-min bins. Within each subject, the dependent variables were averaged for every other bin, so that each averaged time period was separated by a 5-min partition. We used repeated-measures ANOVA models, followed by Bonferroni's t-test, to test differences in \( T_{es} \), sweating rate, and the \( T_{es} \) sweating threshold and slopes due to menstrual phase or oral contraceptive treatment (9). On the basis of an alpha level of 0.05 and a sample size of 8, our beta level (power) was >0.80 for detecting effect sizes of 0.28°C. Data were analyzed with BMDP statistical software (BMDP Statistical Software, Los Angeles, CA) and expressed as means ± SE.

RESULTS

Subject Characteristics

One subject did not have a large luteal phase progesterone peak, so her data were excluded from further analysis. Therefore, all statistical analyses were performed on the remaining eight subjects and only their data are presented. On the pretesting orientation day, the subjects weighed 53.0 ± 3.1 kg, were 162 ± 3 cm tall, their plasma and blood volumes were 2642 ± 258 ml and 74.3 ± 6.6 ml/kg, respectively, and their \( VO_2\text{peak} \) was 34.8 ± 2.1 ml/kg on the recumbent bicycle ergometer. Plasma levels of 17β-estradiol and progesterone were consistent with expected values during the early follicular and midluteal phases of the menstrual cycle and were suppressed during oral contraceptive treatment (Table 1).

Preexercise. During thermoneutral rest, \( T_{es} \) was greater during OC P compared with the follicular phase and OC E + P and was also greater during the luteal phase compared with the follicular phase (Table 1, P < 0.05). Mean \( T_{sk} \) was not affected by menstrual phase or oral...
contraceptive treatment. Based on Hct and [Hb] changes, combined OC treatment (OC E + P) increased plasma volume by ~7.3 ± 3.4% (190 ml, P < 0.05) relative to the follicular phase. However, there were no differences in plasma volume in the luteal phase (approximately ~3.8 ± 2.2%, -115 ml) or OC P treatment (approximately ~0.7 ± 1.8 ml, ~36 ml) compared with the follicular phase. Posm and serum sodium concentration were reduced during exercise during OC E + P relative to the follicular phase (Table 1, P < 0.05). Heart rate, stroke volume, cardiac output, and blood pressure were unaffected by menstrual phase or oral contraceptive treatment before exercise (Table 2).

Passive heating. At the end of 20 min of passive heating, Tsk during OC P was still greater relative to the follicular phase and OC E + P, but there were no differences between the menstrual phases (Fig. 1). Blood Hct and [Hb], Posm, and serum sodium concentration during OC E + P remained below the other trials during passive heating (data are not shown). Passive heating did not increase heart rate, cardiac output, or blood pressure under any of the four conditions (Table 2).

Exercise responses. Exercise increased Tsk during all four trials and remained greatest during OC P (Fig. 2, P < 0.05). Exercise sweating rate was similar across all trials (Fig. 2), but the Tsk threshold for sweating onset was greater during the luteal phase and OC E + P relative to the follicular phase (Table 3, P < 0.05). As with the other time periods, Posm and serum sodium concentration were reduced during OC E + P relative to the other trials (data not shown). Heart rate, stroke volume, cardiac output, and blood pressure increased similarly across trials during exercise (Table 2). Urine sodium losses during the rest, passive heating, and exercise periods were similar across all trials (74.9 ± 22.1, 64.6 ± 17.4, 107.4 ± 29.4, and 73.2 ± 15.5 mEq for follicular and luteal phases, OC E + P and OC P, respectively).

### DISCUSSION

Our major findings are that unopposed progestin administration increased the regulated body temperature as both core temperature and the core temperature threshold for sweating increased and that estrogen administered with progestin reversed these thermoregulatory changes. These effects are likely due to differences in the direct or indirect actions of oral contraceptives on the central nervous system (CNS). Our data support earlier findings that these tempera-
ture effects are independent of peripheral influences on temperature regulation such as body fluid balance (3). This within-subject report addressed potential modulating effects of estrogen on the pronounced progesterone-related increase in regulated body temperature in humans (18, 26), and the results are consistent with previous findings that estrogen lowers the thermoregulatory operating point (33).

Charkoudian and Johnson (7) recently demonstrated that the core temperature threshold for active cutaneous vasodilation during passive heating was increased in women taking oral contraceptives containing estrogen and progestin compared with their responses after 5 days of not taking the pill, a result consistent with earlier findings of increased core temperature threshold for initiation of cutaneous vasodilation during exercise in the luteal phase (18, 31). Postmenopausal women taking combined progestin and estrogen did not exhibit the same reduction in the T_{es} threshold for vasodilation or sweating seen in women taking only estrogen during exercise (2), suggesting that progestin reverses some of the estrogen-related thermoregulatory effects. On the other hand, Chang et al. (5) did not demonstrate a reduction in core temperature after 3 days of estrogen administration to young women in their early follicular phase, perhaps because 3 days of estrogen administration is not long enough to elicit temperature changes or because another hormone, such as FSH, facilitates hypothalamic neuronal adaptation to estradiol. Nonetheless, these reports indicate a disparity between chronic and acute effects of exogenous estrogens and progestins on temperature regulation.

Our data support earlier findings that chronic estrogen with progestin administration does not alter the T_{es} threshold for thermoregulatory effector activation (2). However, our data conflict with other reports in which chronic administration of combined estrogen and progestosterone to young women was associated with greater oral temperature responses to passive heating (6–8). The contrast in our findings may be due to the longer length of time between tests in our study (12–16 wk) compared with the earlier studies (5–7 days). In addition, these earlier studies tested women taking chronic oral contraceptives and compared them with the 5–7 days in the cycle off the pills, whereas we provided an acute treatment to women not taking birth control pills. Either one of these factors may have introduced greater variability into our data and thus type II error.

Our primary hypothesis, that estrogen reverses progestin-related increases in core temperature and thermoregulatory effector response activation, is supported by our data. Estrogen administered along with progestin reduced baseline T_{es} by 0.58°C and the exercise T_{es}
Temperature regulatory responses during 60% VO2peak exercise at 35°C

<table>
<thead>
<tr>
<th>Condition</th>
<th>Follicular</th>
<th>Luteal</th>
<th>OC P</th>
<th>OC E + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(T_{es}) threshold, °C</td>
<td>37.32 ± 0.11</td>
<td>38.02 ± 0.28*</td>
<td>38.07 ± 0.17†</td>
<td>37.46 ± 0.18</td>
</tr>
<tr>
<td>Slope, ΔSR/ΔT_{es}</td>
<td>0.88 ± 0.28</td>
<td>1.08 ± 0.21</td>
<td>1.13 ± 0.30</td>
<td>0.86 ± 0.23</td>
</tr>
<tr>
<td>(r^2)</td>
<td>0.81 ± 0.05</td>
<td>0.90 ± 0.03</td>
<td>0.76 ± 0.05</td>
<td>0.87 ± 0.03</td>
</tr>
</tbody>
</table>

Values are means ± SE. Thermoregulation measured during exercise. \(T_{es}\) for sweating was measured during 40 min of exercise (35°C) in the early follicular and midluteal phases of the menstrual cycle and during administration OC E + P and OC P. *Difference from follicular. †Difference from OC E + P. Differences were considered statistically significant at \(P < 0.05\).
REFERENCES


