Estrogen modifies the temperature effects of progesterone

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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 surge (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 progesterone effects. Estrogen can act on progesterone 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 progesterone 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*, below), and peak oxygen consumption ($\dot{V}o_{2\,peak}$) was determined from an incremental recumbent cycle ergometer test with the use of an automated metabolic cart (Sensor Medics, Yorba Linda, CA).

Each woman participated in four experiments: two baseline heat stress tests and one heat stress test while taking each type of oral contraceptive (two total). Estrogen and progesterone vary across the menstrual cycle, so the study design employed a heat stress test conducted in the early follicular phase, 2–4 days after the beginning of menstrual bleeding (low estrogen and progesterone), and one conducted in the midluteal phase, 7–9 days after the luteinizing hormone peak (high estrogen and progesterone), determined

individually by the use of ovulation prediction kits (Ovu-Quick, Quidel, San Diego, CA). After completing the baseline heat stress tests, the subjects again performed heat stress protocols after 4 wk of either continuous combined (estrogen-progestin, OC E+P) or progestin-only (OC P) oral contraceptive treatment (random assignment). After a 4-wk washout period, the subjects crossed over to the other pill treatment.

During OC E+P, subjects received 0.035 mg of ethinyl estradiol and 1 mg of norethindrone daily. During OC P treatment, subjects received 1 mg/day of norethindrone. To verify phase of the menstrual cycle, plasma levels of estrogen and progesterone were assessed from the preexercise blood sample before the temperature regulation protocol was undertaken.

Heat Stress Tests

Volunteers arrived at the laboratory between 7:00 and 8:00 AM after having eaten only a prescribed low-fat breakfast (~300 kcal). The subjects refrained from alcohol and caffeine for 12 h before the experiment. Blood volumes were not manipulated before any of the experiments, although subjects prehydrated by drinking 7 ml/kg body wt of tap water at home before arrival at the laboratory. On arriving at the laboratory, each subject gave a baseline urine sample, was weighed to the nearest 10 g on a beam balance, and was instrumented for the measurement of cardiac output (see following paragraphs). The subject then sat on the contour chair of a semirecumbent cycle ergometer in the test chamber (27°C, 30% relative humidity). During the control period, the subject was instrumented for the measurement of esophageal (T_{es}) and skin (T_{sk}) temperatures, sweat rate, and blood pressure. An indwelling catheter (21-gauge) was inserted into an arm vein for blood sampling, and a heparin block (20 U/ml) maintained catheter patency. Subjects were semirecumbent during placement of the catheter and were seated for 45 min before sampling to ensure a steady state in plasma volume and constituents. Resting blood pressure (Colin Medical Instruments, 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 $\dot{V}o_{2\,peak}$ 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 (15) 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 two around the torso. The distance between the inner tapes was measured and made identical for all four experiments. Cardiac stroke volume was calculated by using the equation of Kubicek et al. (19) and was averaged (ensemble averaging) over 25 s.

All blood samples were analyzed for hematocrit (Hct), the concentrations of Hb ([Hb]) and total protein ([TP]), plasma osmolality (Posm), and serum concentrations of sodium and potassium. The control blood samples were also analyzed for 17β-estradiol ($P_{[E2]}$) and progesterone ($P_{[P4]}$) concentrations.

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. All other aliquots were placed in chilled tubes containing EDTA. The samples containing EDTA were analyzed for $P_{[E2]}$ and $P_{[P4]}$ and were centrifuged, frozen immediately, and stored at $-80°C$ until analysis. All urine samples were analyzed for volume, osmolality, and sodium and potassium.

Serum and urine sodium and potassium were measured by flame photometry (Instrumentation Laboratory, Model 943). Posm and urine osmolality were assessed by freezing point depression (Advanced Instruments 3DII). Plasma concentrations of $P_{[E2]}$ and $P_{[P4]}$ were measured by RIA. Intra- and interassay coefficients of variation for the midrange standard for $P_{[E2]}$ (58 ± 4 pg/ml) were 15% and 4% (Diagnostic Products, Los Angeles, CA) and for $P_{[P4]}$ (1.7 pg/ml) were 14% and 6% (Diagnostic Products).

Blood Volume

Absolute blood volume was measured by dilution of a known amount of Evans blue dye dilution. This technique involves injection of an accurately determined volume of dye (by weight, because the specific density is 1.0) into an arm vein and taking blood samples for determination of dilution after complete mixing (10, 20, and 30 min). Plasma volume was determined from the product of the concentration and volume of dye injected divided by the concentration in plasma after mixing, taking into account 1.5% lost from the circulation within the first 10 min. Blood volume was calculated from plasma volume and Hct corrected for peripheral sampling (13).

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

%ΔPV
$$= 100[[(Hb_b)/(Hb_a)][(1 - Hct_a \cdot 10^{-2})]/[(1 - Hct_b \cdot 10^{-2})]] - 100$$

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 $\dot{V}O_{2\,peak}$ 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 compared with the follicular phase (Table 1, $P < 0.05$). Mean T_{sk} was not affected by menstrual phase or oral

Table 1. *Baseline subject characteristics and responses to passive heating and 40 min of exercise in the heat*

	Follicular	Luteal	OC P	OC E+P
BW, kg	53.8 ± 3.3	53.2 ± 3.0	53.3 ± 2.9	52.1 ± 3.1
$P_{[E2]}$, pg/ml	23.5 ± 4.6	85.4 ± 21.9	31.3 ± 10.0	10.0 ± 2.9
$P_{[P4]}$, ng/ml	0.7 ± 0.1	12.0 ± 1.8	0.6 ± 0.1	0.7 ± 0.1
Hct, %	38.3 ± 0.7	39.3 ± 0.5*†	38.9 ± 0.5	37.8 ± 0.7
[Hb], g/dl	13.1 ± 0.3†	13.4 ± 0.2†	13.1 ± 0.2†	12.3 ± 0.3
Posm, mosmol/kg	284 ± 1	283 ± 1	285 ± 1	282 ± 1*
$S_{[Na+]}$, meq/l	137.8 ± 0.8	137.4 ± 0.5	138.0 ± 0.7	136.8 ± 0.9
$P_{[P4]}/P_{[E2]}$	30.1 ± 3.8	166.0 ± 56.1		
T_{es}, °C at 27°C	36.68 ± 0.21	37.08 ± 0.21*	37.60 ± 0.31*	37.04 ± 0.23
T_{sk}, °C at 27°C	31.27 ± 0.38	31.68 ± 0.16	31.76 ± 0.19	31.82 ± 0.27
T_{es}, °C at 35°C preexercise	36.71 ± 0.17	37.20 ± 0.24*	37.65 ± 0.24*†	36.74 ± 0.14
T_{sk}, °C at 35°C preexercise	35.08 ± 0.29	35.04 ± 0.14	35.21 ± 0.15	35.45 ± 0.20
T_{es}, °C at 35°C 40 min of exercise	37.88 ± 0.17	38.32 ± 0.27*†	38.73 ± 0.34*†	37.75 ± 0.21
T_{sk}, °C at 35°C 40 min of exercise	34.82 ± 0.26	34.99 ± 0.41	34.60 ± 0.07	35.25 ± 0.21

Values are means $\pm$ SE. Subject characteristics were measured at 27°C and after passive heating (35°C) and exercise in the heat (35°C). Preexercise body weight (BW), plasma concentrations of endogenous 17β-estradiol ($P_{[E2]}$) and progesterone ($P_{[P4]}$), hematocrit (Hct), blood hemoglobin concentration ([Hb]), plasma osmolality (Posm), and serum sodium concentration ($S_{[Na+]}$) are shown. Esophageal (T_{es}) and skin (T_{sk}) temperatures in the early follicular and midluteal phases of the menstrual cycle and during administration of combined (estradiol + progestin, OC E + P) and (progestin only, OC P) oral contraceptive pills are also shown at rest and after 40 min of exercise at 35°C. * Difference from follicular. † Difference from OC E + P. Differences were considered statistically significant at $P < 0.05$.

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 before exercise during OC E+P relative to the follicular phase (Table 1, $P < 0.05$). Heart rate, stroke volume, cardiac output, and blood

Table 2. *Cardiovascular responses to passive heat and exercise*

	Rest (27°C)	Rest (35°C)	Exercise 35°C (20 min)	Exercise 35°C (40 min)
Heart rate, bpm				
Follicular	67 ± 3	69 ± 3	132 ± 8	140 ± 8
Luteal	67 ± 3	69 ± 4	127 ± 7	137 ± 7
OC P	66 ± 3	68 ± 3	131 ± 6	141 ± 7
OC E + P	64 ± 4	67 ± 4	126 ± 10	135 ± 9
Stroke volume, ml				
Follicular	81 ± 8	80 ± 7	98 ± 10	99 ± 10
Luteal	88 ± 8	88 ± 7	111 ± 11	111 ± 10
OC P	87 ± 6	87 ± 6	113 ± 10	110 ± 11
OC E + P	99 ± 7	95 ± 8	112 ± 8	115 ± 15
Cardiac output, l/min				
Follicular	5.3 ± 0.4	5.5 ± 0.4	12.9 ± 1.1	13.6 ± 1.2
Luteal	5.8 ± 0.5	6.0 ± 0.3	13.9 ± 1.2	14.9 ± 1.4
OC P	5.8 ± 0.4	6.0 ± 0.3	14.4 ± 0.9	15.2 ± 1.4
OC E + P	6.4 ± 0.5	6.2 ± 0.5	13.6 ± 1.0	15.1 ± 1.4
Mean arterial pressure, mmHg				
Follicular	80 ± 4	81 ± 4	90 ± 4	92 ± 5
Luteal	80 ± 3	78 ± 3	92 ± 4	90 ± 5
OC P	78 ± 2	76 ± 2	88 ± 2	89 ± 2
OC E + P	77 ± 2	78 ± 2	93 ± 5	96 ± 5

Values are means $\pm$ SE. Heart rate, stroke volume, cardiac output, and mean arterial pressure values were measured at rest (27°C) and in response to 20 min of passive heating (35°C) and 40 min of exercise (35°C) in the follicular and luteal menstrual phases.
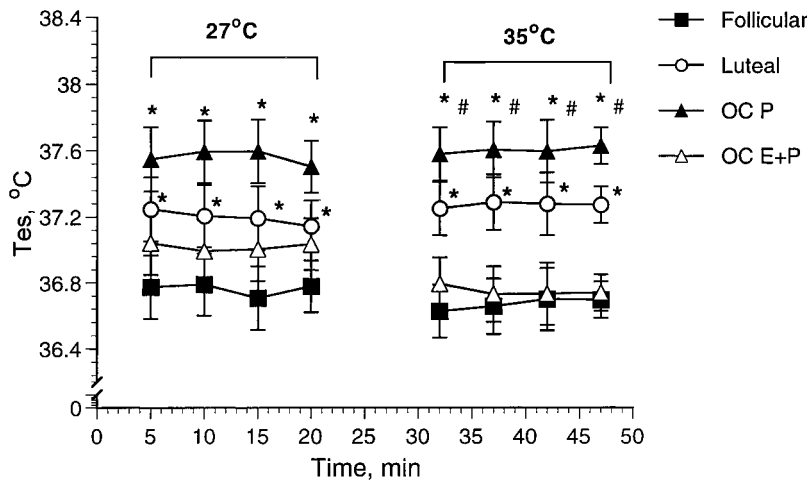
pressure were unaffected by menstrual phase or oral contraceptive treatment before exercise (Table 2).

Passive heating. At the end of 20 min of passive heating, T_{es} 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 T_{es} 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 T_{es} 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-

Fig. 1. Esophageal temperature (T_{es}) during 20-min rest at 27°C and during 20-min passive heating at 35°C. * Different from follicular phase. # Different from combined estrogen-progestin oral contraceptive administration (OC E+P). Differences considered significant at $P <$ 0.05. OC P, progestin-only oral contraceptive administration.

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 progesterone 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}
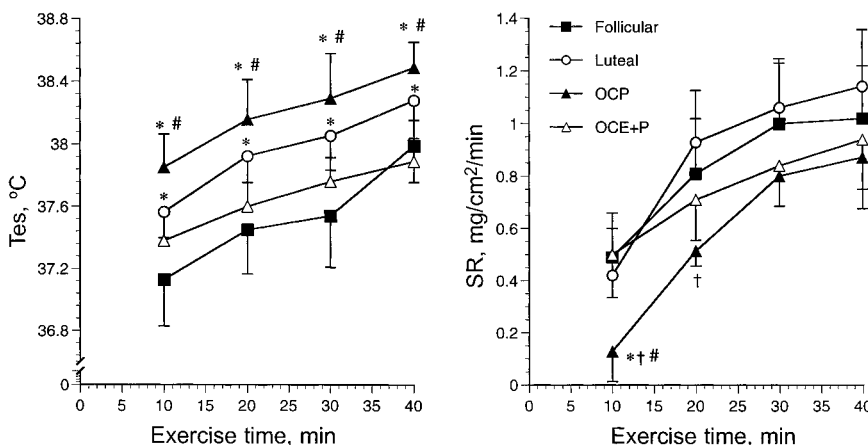

Fig. 2. T_{es} and arm sweat rate (SR) during 40 min of semirecumbent cycle exercise in the heat (35°C). * Different from follicular phase. † Different from luteal phase. # Different from OC E+P. Differences considered significant at $P < 0.05$.

Table 3. *Temperature regulatory responses during 60% $\dot{V}o_{2peak}$ exercise at 35°C*

	Follicular	Luteal	OC P	OC E + P
T_{es} threshold, °C	37.32 ± 0.11	38.02 ± 0.28*	38.07 ± 0.17*†	37.46 ± 0.18
Slope, $\Delta SR/\Delta T_{es}$	0.88 ± 0.28	1.08 ± 0.21	1.13 ± 0.30	0.86 ± 0.23
r^2	0.81 ± 0.05	0.90 ± 0.03	0.76 ± 0.05	0.87 ± 0.03

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 $P < 0.05$.

threshold for sweating by 0.68°C compared with progestin-only administration, indicating a profound modifying role for estrogen on the progesterone-induced core temperature increase. We suspect that the actions of these hormones occur via direct effects in the preoptic/anterior hypothalamus, the primary temperature regulation area of the brain. Both estrogen and progesterone readily cross the blood-brain barrier and may modulate thermoregulation via action in the CNS, and sex steroid receptors have important effects on thermosensitive neurons in the brains of animals (24, 27). Progesterone inhibits warm-sensitive neuron activity, thus inhibiting heat-loss mechanisms and increasing body temperature (24). Conversely, estrogen inhibits cold and stimulates warm-sensitive neurons (27), and should therefore inhibit heat-retaining mechanisms, excite heat loss mechanisms, and thus cause a decrease in the regulated body temperature. Although we did not test CNS mechanisms for the temperature effects, sex steroids are unlikely to act via a secondary mediator or pathway, such as cytokines (4) or heat shock proteins. These indirect mechanisms have been essentially ruled out as possible mediators in recent investigations in which neither interleukin-1β nor interleukin-6 was elevated during OC E+P administration to young women (25), the temperature responses were unaffected by PG inhibition with ibuprofen (6), and heat-shock proteins were unchanged during heating in young women given estrogen (5).

Although direct actions within the CNS are the primary mechanism by which progesterone and estrogen exert their effects on the temperature regulation systems, the regulation of body temperature in humans also interacts with systems that regulate the volume and osmotic pressure of the extracellular fluid (22). Blood volume expansion improves the efficiency of cardiovascular and thermoregulatory responses during physical activity. When blood volume is expanded, cardiac stroke volume increases, resulting in elevated cardiac output and improved ability to deliver blood to muscle and skin simultaneously, where heat transfer takes place. During the menstrual cycle (32) and during short-term estrogen administration (29, 34), high estrogen levels in the blood are associated with plasma volume expansion. In this investigation, plasma volume appeared lowest during the midluteal phase of the menstrual cycle coinciding with the highest core temperature and delayed sweating onset during exercise. However, although OC E+P was associated with a large increase in plasma volume compared with the follicular phase, there were no differences in the thermo-

regulatory responses during exercise and no increase in stroke volume associated with OC E+P. Finally, although plasma volume was greater during OC E+P compared with OC P, again, stroke volume did not increase with OC E+P, suggesting that these plasma volume increases had little impact on heat loss mechanisms (11).

Finally, our findings are limited by our inability to measure exogenous progestins and their metabolites, so plasma progesterone does not reflect the true levels of progestins during oral contraceptive administration. Therefore, we recognize that comparison of the different pill preparations is tenuous because the relative potency of synthetic estrogens and progestins found in oral contraceptives on the temperature regulation system is unknown. Furthermore, synthetic estrogens and progestins are metabolized at different rates among individual women so we are limited in our ability to predict the level of these hormones actually acting on tissue simply by knowing the quantity of the hormone administered.

We found that oral contraceptive pills containing estrogen with progestin did not produce the thermoregulatory effects of oral contraceptive pills that contained only progestin. This estrogen-related reversal of the thermoregulatory actions of progestin is most likely due to specific effects on thermosensitive neurons in the CNS. These results confirm earlier findings that estrogen lowers the thermoregulatory operating point (33). Our findings differed from previous findings in young women taking chronic oral contraceptives in that we did not find that oral contraceptives containing both estrogen and progestin significantly increased core temperature at baseline or after passive heating (6–8). Finally, although estimated plasma volume was lower during administration of progestin alone compared with combined estrogen and progestin administration, exercise stroke volume was unchanged, supporting earlier findings that plasma volume change is not a major contributor to altered temperature regulation during oral contraceptive administration (2).

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