Estrogen and Cortisone: Effects on Thermoregulation in the Female Rabbit[1] (34733)

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Estrogen and cortisone are reported to have a temperature depressing effect in man (1–3), but their mechanism of action in producing hypothermia is not established. The effect of cortisone on the febrile response of rabbits (4) and dogs (5) to endogenous pyrogens such as leukocytic and hepatic pyrogens has also been studied but little, if anything, is known about estrogen in this regard.

The purpose of this paper is to describe the effect of estrogen and cortisone on the basal body temperature of the female rabbit and the effect of estrogen on their febrile response to leukocytic pyrogen.

Materials and Methods. Adult New Zealand female rabbits weighing approximately 2.0 kg at the onset of the experiments were used. The animals were housed in separate cages and all studies were performed in air-conditioned rooms maintained at 70°F. Oophorectomies were performed on one group of animals under sterile conditions using Nembutal anesthesia. These animals were treated postoperatively with a combination of procaine penicillin G (100,000 units) and streptomycin sulfate (0.125 g) administered intramuscularly as a 0.5 ml suspension each day for 3 days. The oophorectomized animals were permitted to recover for at least 1 week prior to their use in any experiments.

Body temperature was determined by measuring rectal temperatures using a Yellow Springs Telethermometer. All rectal temperatures were recorded daily between 1:30 and 3:30 p.m. following a period of acclimitization of the animals to their stalls.

Estradiol benzoate (Schering's Progynon benzoate; 1.0 mg/ml) was injected subcutaneously in a dose of 100 μg/animal/day (0.1 ml) and cortisone acetate (Upjohn's aqueous suspension; 25 mg/ml) was administered intramuscularly as two 25-mg portions (1.0 ml) spaced approximately 12 hr apart. Sesame oil (0.1 ml) and normal saline (0.2 ml) administered subcutaneously and intramuscularly, respectively, were given to the control animals. A dose of 100 μg/day of estradiol benzoate was chosen because such a dose has been demonstrated to have an effect on brain thresholds in the rabbit (6). The 50-mg/day dose of cortisone acetate was chosen because of the known antipyretic effect of such a dose in the rabbit (4).

Leukocytic pyrogen (LP) was prepared from exudate cells as previously described (7) and 2–4 ml were administered intravenously depending upon the relative strength of the batches of pooled pyrogen. Fever indices (FI) were determined planimetrically by measuring the area under a 2-hr fever curve.

Results. Effect of estradiol benzoate on basal body temperature. Female rabbits were given estradiol benzoate over an 8-day period. Mean temperatures during five estrogen-treatment days were compared to the mean temperatures of the two pretreatment days giving a total of 10 comparisons and using a $p<0.05$ as the lower limit of significance these showed that there was a highly significant depression of basal body temperature during the estrogen-treatment period (9 comparisons with $p<0.001$ and 1 comparison with $p<0.005$). On 3 of 5 days during estrogen treatment a significant depression ($p<0.01$, 0.025, and 0.01) of basal temperature compared to corresponding sesame controls was observed (Fig. 1). Sesame controls also showed some depression of basal temperature

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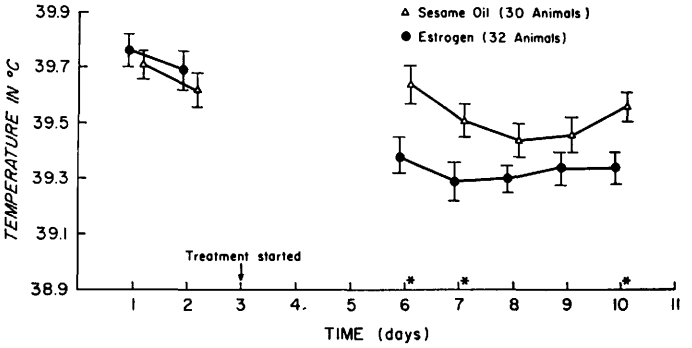

FIG. 1. Effect of estrogen on basal temperature of normal female rabbits: Each point represents the mean of the appropriate number of observations for the respective groups (shown in parentheses). *Indicates days on which estrogen (estradiol benzoate)- and sesame oil-treated groups showed statistically significant differences (day 6, $p < 0.01$; day 7, $p < 0.025$; day 10, $p < 0.01$). All p values for experiments presented in this paper were determined by Student's t test; and brackets in all experiments indicate the SEM.

compared to their two preinjection mean temperatures but only 5 of 10 comparisons showed statistical significance ($p<0.05$, 0.05, 0.02, 0.005 and 0.001).

Effect of cortisone acetate on basal body temperature. Female rabbits given cortisone acetate over an 8-day period showed a significant elevation of basal body temperature on the fourth, fifth, and sixth treatment days (sixth, seventh, and eighth experimental days) compared to the two preinjection recordings ($p<0.01$, 0.005, 0.001, 0.005, 0.001, and 0.001) and saline-injected controls ($p<0.05$, 0.01, and 0.02). Saline controls showed no difference between basal body temperature recordings made during the injection period and preinjection temperatures (Fig. 2). Blood leukocytes obtained from the cortisone-treated animals on the sixth treatment day (eighth experimental day) were suspended in isotonic phosphate buffered saline in varying cell concentration between 9 $\times$ 10^6 and 3 $\times$ 10^7 cells/ml of suspension and were incubated at 37° for 18 hr. Following incubation the supernatant was injected into rabbits to ascertain whether such cells

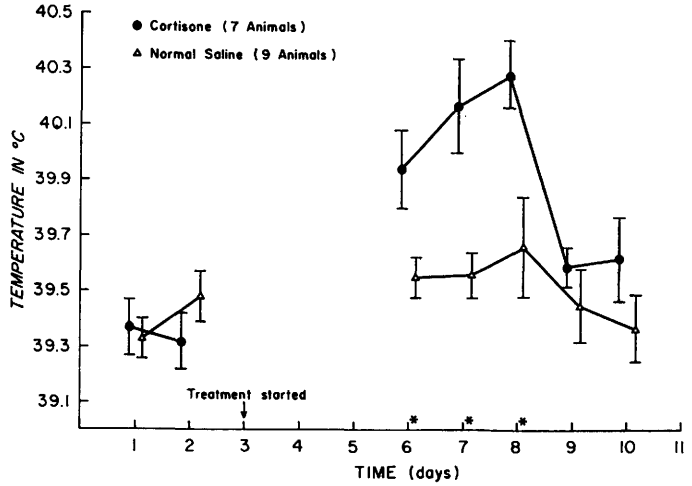

FIG. 2. Effect of cortisone on basal temperature of normal female rabbits: *Indicates days on which the cortisone acetate injected group and normal saline injected controls showed significant differences in mean basal body temperature (day 6, $p < 0.05$, day 7, $p < 0.01$, day 8, $p < 0.02$).

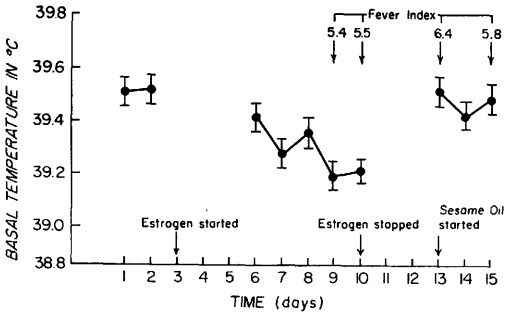

FIG. 3. Estrogen treatment of oophorectomized rabbits. Each point represents the mean basal body temperature of 13 rabbits. Fever index expressed over appropriate day represents the mean of 13 determinations. The SEM for each fever index include; 5.4 ± 0.5; 5.5 ± 0.4; 6.4 ± 0.5; and 5.8 ± 0.6. Basal body temperatures on days 9 and 10 showed significant differences compared to days 13 and 15 ($p < 0.005$, 0.001, 0.01, and 0.01) but fever indices on same days did not.

were releasing LP. No LP was detectable in any sample.

Effect of estradiol benzoate on response to LP: Two groups of female rabbits treated with either estradiol benzoate or sesame oil as previously described were given LP on the tenth experimental day. Although the estrogen-treated animals showed a significantly lower basal body temperature they did not show any difference in their response to LP compared with controls. Oophorectomized animals were similarly treated with estradiol benzoate for 8 days and on the ninth and tenth experimental days were given LP. The estrogen treatment was stopped after the eighth treatment and sesame oil was substituted on the recording days. The animals' basal body temperatures which had been depressed during estrogen treatment returned to preinjection levels following estrogen withdrawal but their response to LP did not vary significantly (Fig. 3).

Discussion. The action of estrogen in inducing hypothermia should include consideration of an effect on the hypothalamic centers concerned with thermoregulation or on the peripheral mechanisms involved in heat conservation and generation. In reviewing the literature one can find evidence to show that estrogen has an effect on: (i) Mammalian anterior hypothalmic/preoptic centers (8, 9), which is an area known to be concerned with thermoregulation (10, 11). (ii) On blood vessels (12, 13) which play an important role in heat conservation and dissipation. (iii) On thyroid function (14, 15) one parameter of which is heat generation (16, 11). Rothchild and Barnes (17) have implied that the estrogen hypothermic effect is mediated through a direct effect on cutaneous blood vessels; however, possible effects on hypothalamic centers and/or other parameters of thermoregulation should not be dismissed. This paper provides an experimental model using the rabbit for pursuing such studies.

The hyperthermic effect of cortisone acetate observed in this experiment is just the opposite of what was observed in man (3). There are several ways one might explain this, including differences in species and laboratory versus clinical observations. In any event, it seems that this hyperthermic effect is a primary result of the hormone and not secondary to a bacteremia or endotoxemia since their blood leukocytes were not releasing LP.

Although cortisone and estrogen display opposite effects in the rabbit with respect to body temperature, neither cortisone as indicated by previous experiments (4) nor estrogen as indicated by this experiment is capable of significantly influencing the pyrogenic response to LP. This observation suggests that the thermoregulatory centers or aspects of thermoregulation concerned with controlling basal body temperature are independent of those concerned with the hyperthermic response to nonbacterial pyrogens. The observation of others with regard to the pyrogenic effect of progesterone in estrogen-treated subjects (17) is compatible with this. However, our data concerning the effect of estrogen on thermoregulation do not support the implication of Rothchild and Barnes (17) that it is mediated through a direct effect on cutaneous blood vessels. If the blood vessels concerned with heat conservation were affected directly and significantly by estrogen, then one might expect to see quantitative differences in the febrile response to LP since

hyperthermia induced by LP (18) is mediated primarily through peripheral vasoconstriction in the rabbit.

The fact that sesame oil-treated animals showed some depression of their basal body temperature whereas normal saline-treated animals did not was noted, but we cannot offer any explanation at this time.

Summary. Estrogen in the form of estradiol benzoate and cortisone as the acetate are shown to have an effect on thermoregulation in the female rabbit. Estrogen causes a significant, consistent depression of basal body temperature and cortisone causes a transient hyperthermia. Conversely, neither of these hormones is capable of significantly influencing the thermoregulatory response of the rabbit to leukocytic pyrogen.

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