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The Role of Prolactin in Reproductive Failure Associated with Heat Stress in the Domestic Turkey[1]

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ABSTRACT

Reproductive failure associated with heat stress is a well-known phenomenon in avian species. Increased prolactin (PRL) levels in response to heat stress have been suggested as a mechanism involved in this reproductive malfunction. To test this hypothesis, laying female turkeys were subjected to 40°C for 12 h during the photo-phase daily or maintained at 24–26°C. Birds in each group received oral treatment with parachlorophenyalanine (PCPA; 50 mg/kg BW/day for 3 days), an inhibitor of serotonin (5-HT) biosynthesis, or immunized against vasoactive intestinal peptide (VIP). Both treatments are known to reduce circulating PRL levels. Nontreated birds were included as controls. In the control group, high ambient temperature terminated egg laying, induced ovarian regression, reduced plasma luteinizing hormone (LH) and ovarian steroids (progesterone, testosterone, estradiol) levels, and increased plasma PRL levels and the incidence of incubation behavior. Pretreatment with PCPA reduced ($P < 0.05$) heat stress-induced decline in egg production, increase in PRL levels, and expression of incubation behavior. Plasma LH and ovarian steroid levels of heat stressed birds were restored to that of controls by PCPA treatment. As in PCPA-treated birds, VIP immunoneutralization of heat-stressed turkeys reduced ($P < 0.05$) circulating PRL levels and prevented the expression of incubation behavior. But it did not restore the decline in LH, ovarian steroids, and egg production ($P > 0.05$). The present findings indicate that the detrimental effect of high temperature on reproductive performance may not be related to the elevated PRL levels in heat-stressed birds but to mechanism(s) that involve 5-HT neurotransmission and the induction of hyperthermia.

birds, egg production, heat stress, incubation behavior, luteinizing hormone, ovary, pituitary hormones, prolactin, reproduction, reproductive hormones, serotonin, stress, turkeys, vasoactive intestinal peptide

INTRODUCTION

Reproductive failure associated with environmental heat stress in birds is a well-known phenomenon, but the physiological basis is far from clear. Many studies have examined the interrelationship between elevated temperature and cessation of egg and semen production in birds [1, 2]. One suggestion was that the reproductive failure associated with heat stress was due to a reduction in ovarian blood supply because of peripheral vasodilatation [3]. In addition, reduced food consumption may account for some of the impairment in reproduction. However, the effect of high environmental temperatures upon the rate of egg laying appeared largely unrelated to food intake [4–6]. The regulatory mechanisms for the reduced reproductive efficiency in the heat-stressed hen might be modulated by both the hypothalamus and pituitary [7–12], and/or by the ovary, as in mammals [13].

Previous studies demonstrated that stress, in a number of forms and in different species, both increased and decreased circulating prolactin (PRL) and gonadotropins (LH, FSH), respectively in rats [14–16], cows and goats [17, 18], turkey poults [19], laying chickens [20], and turkey hens [21]. Furthermore, PRL is known to induce incubation behavior in turkey hens [22, 23] and evidence shows that the expression of incubation behavior is increased by heat stress [8]. Taken together, this suggests a close relationship between termination of egg production, elevated PRL levels, incubation behavior, and exposure to high temperature. Because reducing PRL levels and termination of incubation behavior can be achieved by either active immunization against vasoactive intestinal peptide (VIP), the avian PRL-releasing factor [24, 25] or by oral administration of parachlorophenyalanine (PCPA), an inhibitor of serotonin (5-HT) biosynthesis [26], the present study investigated whether either of these two methods might prevent the reproductive failure associated with heat stress in turkey hens.

MATERIALS AND METHODS

Experimental Animals

Thirty-six turkey hens of British United Turkey strain (Yaffe Hod, Israel) at 25 wk of age were divided to two treatment groups by body weight (BW; n = 18, BW = 11.1 ± 1.4 kg). Birds were housed in two environmentally controlled rooms (20 m^2) equipped with nest boxes. Birds were held under nonphotostimulatory conditions (6L:18D) with light intensity of 0.1 W/m^2 at the level of the birds head achieved by warm, white fluorescent lamps. Feed and water were provided ad libitum. At 31 wk of age, birds were photostimulated by increasing the light period to 16 h of light (16L:8D).

Experiment 1

Temperature treatments. At 36 wk of age, birds in one room were subjected to 40°C for 12 h, during the photo phase, daily (H), then returned to thermoneutral condition for the rest of the day. Birds in the second room remained under thermoneutral conditions (24–26°C; N).

PCPA treatments. One week after the initiation of temperature treatments, at 37 wk of age, birds in each room were divided to two subgroups

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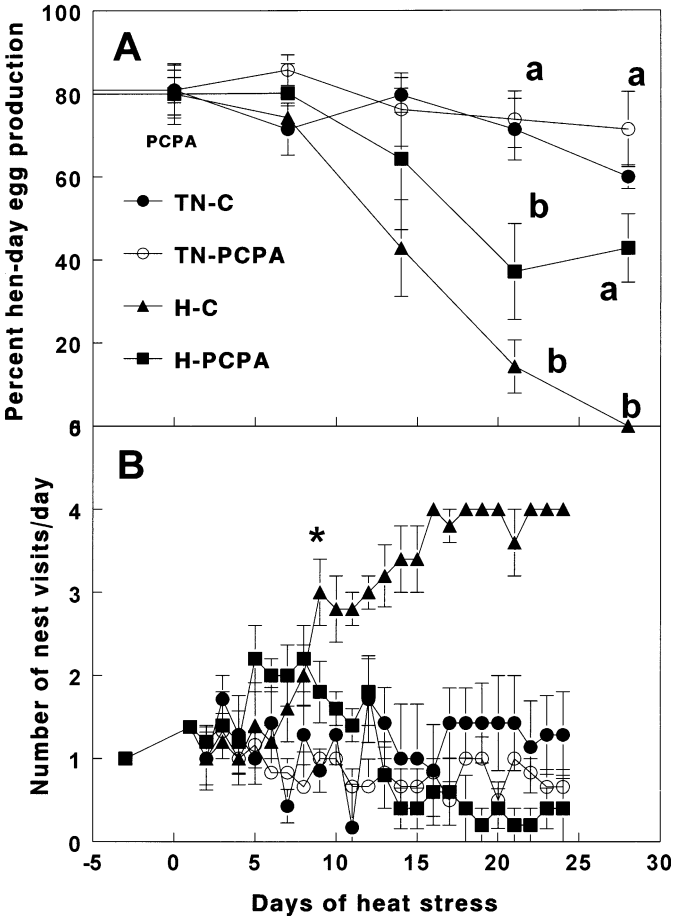

FIG. 1. Percent hen-day egg production (**A**) and nesting activity (**B**) of large, white female turkeys exposed to high environmental temperature (40°C; H-C) or maintained under 24–26°C (N-C) and treated with PCPA (H-PCPA, N-PCPA). Data are presented as mean ± SEM. Values with different letters (a, b) are significantly different ($P < 0.05$) on the same day. Data marked with * are significantly different during the duration of the experiment.

(n = 9); the first subgroup received PCPA in gelatin capsules orally (50 mg/kg BW/day for 3 days; H-PCPA and N-PCPA), and the second subgroup in each room received empty gelatin capsules orally (H-C, and N-C). Two weeks after the initiation of temperature treatments, the PCPA treatment was repeated using the same procedure. The experiment was terminated when birds reached 41 wk of age.

Egg production and nesting activity were recorded daily. Nesting activity was recorded four times a day. A bird that was found four times a day in the nest without laying an egg was considered incubating. Heparinized blood samples were drawn from the brachial vein for determining plasma PRL, LH, progesterone, estrogen, and testosterone levels, 3 days before initiation of heat stress. Thereafter, blood samples were drawn every other day until 39 wk of age and every week until 41 wk of age.

Experiment 2

The experimental design and the number of birds per treatment were similar to that described in experiment 1 excepting four treatment groups were included and subjected to 40°C for 12 h during the photo phase, daily (H), or remained under 24–26°C (N).

Treatment groups were 1) untreated control (H-C and N-C, for high temperature and thermoneutral rooms, respectively), 2) PCPA-treated birds (PCPA was given orally at the beginning of heat stress exposure and 14 days later; H-PCPA and N-PCPA for high temperature and thermoneutral rooms, respectively), 3) actively immunized against VIP, (H-VIP and N-VIP for high temperature and thermoneutral rooms, respectively), and 4) actively immunized against VIP plus oral administration of PCPA (H-PCPA+VIP and N-PCPA+VIP for high temperature and thermoneutral rooms, respectively). Active immunization against VIP was conducted according to a previously described method [25, 27].

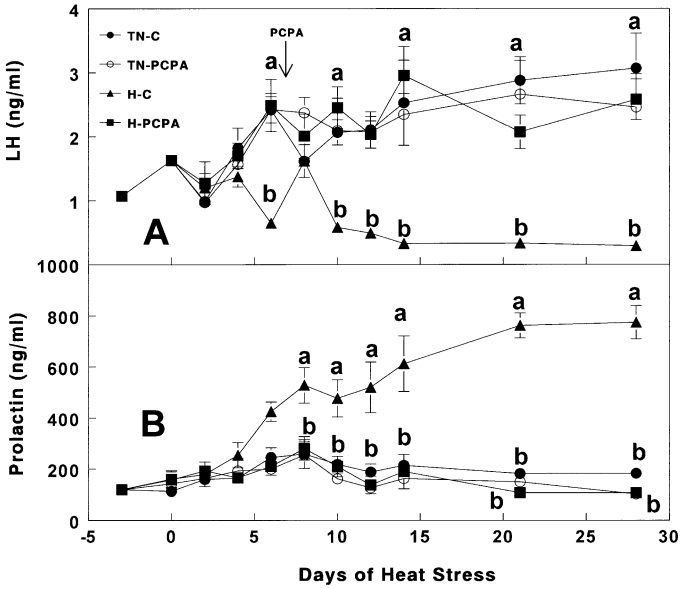

FIG. 2. Plasma LH (**A**) and prolactin levels (**B**) of large, white female turkeys exposed to high environmental temperature (40°C; H-C) or maintained under 24–26°C (N-C) and treated with PCPA (H-PCPA, N-PCPA). Data are presented as mean ± SEM. Values indicated with different letters on the same day are significantly different ($P < 0.05$).

All procedures were approved by the Animal Care and Welfare Committee of The Hebrew University of Jerusalem.

Hormone Analysis

Plasma PRL level was determined by radioimmunoassay according to a previously described method [28]. The interassay coefficient of variation was 5%. Plasma-LH level was measured according to a previously described method [29]. The interassay coefficient of variation was 7%. Plasma progesterone, estrogen, and testosterone were measured by an enzyme-linked immunosorbent assay [30].

Statistical Analysis

Data was analyzed by two-way analysis of variance (temperature vs. hormonal treatments) using JMP software (SAS Institute, Cary, NC). Data are presented as means and standard errors of the mean. Hormonal data were analyzed on models based on repeated measurements.

RESULTS

Experiment 1

A significant ($P < 0.05$) reduction in egg production was observed 15 days after initiation of heat stress (Fig. 1A) and was completely abolished 13 days later in the H-C group. Egg production in the H-PCPA birds was significantly reduced ($P < 0.05$) after 22 days of heat exposure; thereafter, however, egg production increased and was not significantly ($P > 0.05$) different from that of N-C or N-PCPA birds. Nesting activity was increased in H-C birds 8 days after initiation of heat stress, and all H-C birds expressed incubation behavior by the end of the experiment (Fig. 1B).

Heat stress caused a significant reduction in plasma LH level by Day 5 (Fig. 2A, $P < 0.05$) and a significant elevation in plasma PRL levels by Day 8 (Fig. 2B, $P < 0.05$) of temperature treatment in H-C birds. PCPA treatment prevented the heat-induced decline and increase in plasma LH and PRL levels, respectively. Plasma progesterone (Fig. 3A), testosterone (Fig. 3B), and estrogen (Fig. 3C) levels were significantly ($P < 0.05$) reduced by heat stress only

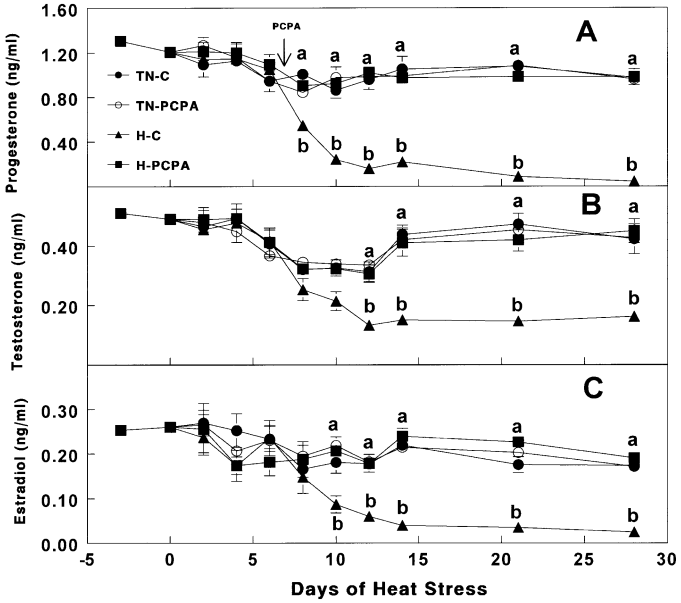

FIG. 3. Plasma progesterone (**A**), testosterone (**B**), and estrogen (**C**) of large, white female turkeys exposed to high environmental temperature (40°C; H-C) or maintained under 24–26°C (N-C) and treated with PCPA (H-PCPA, N-PCPA). Data are presented as mean ± SEM. Values indicated with different letters on the same day are significantly different ($P < 0.05$).

in the H-C group; birds exposed to heat stress and treated with PCPA did not exhibit a decline in their plasma steroid levels.

Experiment 2

There was no reduction ($P > 0.05$) in egg production detected in H-C, H-VIP, and H-PCPA birds by Day 8 of heat stress (Fig. 4B). Egg production was terminated by

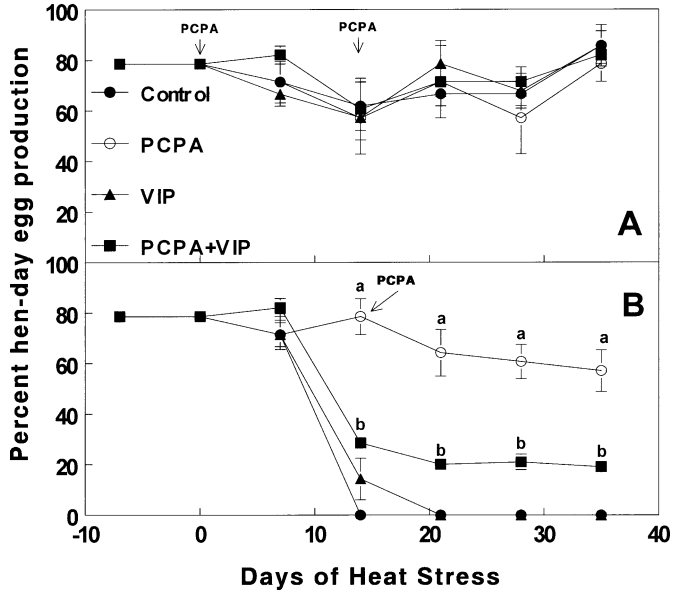

FIG. 4. Percent hen-day egg production of large, white female turkeys maintained under thermoneutral conditions (**A**) or exposed to high environmental temperature (**B**). Birds were treated with PCPA (PCPA), were actively immunized against VIP (VIP), received a combination of PCPA and active immunization against VIP (PCPA+VIP), or were untreated (control). Data are presented as mean ± SEM. Values indicated with different letters on the same day are significantly different ($P < 0.05$).

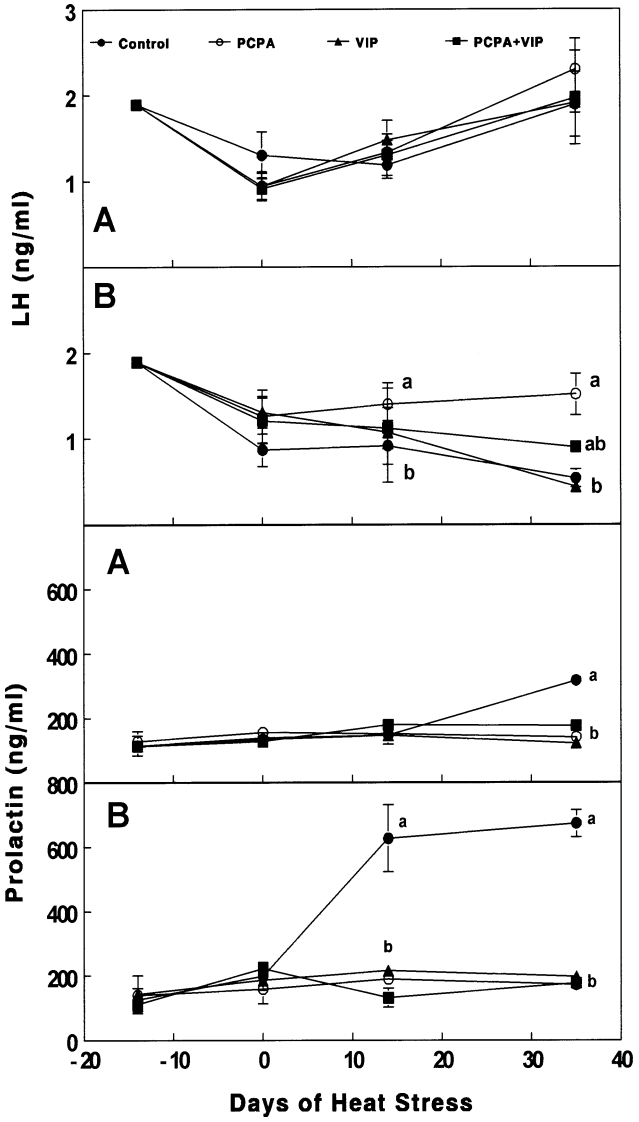

FIG. 5. Plasma LH/PRL of large, white female turkeys exposed to high environmental temperature (**A**) or maintained under thermoneutral conditions (**B**). Birds were treated with PCPA (PCPA), were actively immunized against VIP (VIP), received a combination of PCPA and active immunization against VIP (PCPA+VIP), or were untreated (control). Data are presented as mean ± SEM. Values indicated with different letters on the same day are significantly different ($P < 0.05$).

Day 14 after initiation of heat stress in H-C birds and by Day 21 in H-VIP birds. Egg production of the H-PCPA group was similar ($P > 0.05$) to that of control thermoneutral birds (Fig. 4A). Hens that received the combined PCPA+VIP treatment and subjected to heat stress (H-PCPA+VIP) continued to lay but at a significantly lower rate than the H-PCPA-treated group.

There were no significant differences in plasma LH levels in birds reared under thermoneutral conditions (Fig. 5A). In contrast, a significant reduction in plasma LH levels were detected by Day 14 in the H-C group and by the end of the experiment in the H-VIP group (Fig. 5B). Plasma PRL levels were significantly increased by Day 35 in the N-C group compared with that of other thermoneutral treatment groups (Fig. 5A). Fourteen days after initiation of heat stress, a significant increase in plasma PRL level was detected in the H-C group (Fig. 5B) but not in the other high-temperature treatment groups.

Plasma progesterone concentrations did not differ among treatment groups under thermoneutral conditions (Fig. 6A), but levels varied ($P < 0.05$) in heat-exposed birds. The heat-induced decrease in progesterone was less pronounced in the H-PCPA group when compared with that of the other treatment groups (Fig. 6B). Similarly, plasma testosterone levels (Fig. 6) decreased in all treatments, but no treatment differences were found under thermoneutral conditions (Fig. 6A). Plasma testosterone levels were lower in H-C, H-VIP, and H-PCPA+VIP groups than in the PCPA group by Day 14 of heat stress treatment (Fig. 6B). There were no significant differences in plasma estrogen levels in birds reared under thermoneutral conditions (Fig. 6A); however, lower plasma estrogen levels were observed by Day 14 of heat stress in the H-C- and H-VIP-treated birds when compared with the PCPA-treated group (Fig. 6B).

DISCUSSION

The results of the present study revealed that high ambient temperatures accelerated the increase in circulating PRL and expression of incubation behavior in laying female turkeys, while suppressing plasma LH and ovarian steroid levels, and shortening the egg-laying period. Treatment with PCPA, which inhibits 5-HT synthesis and lowers central 5-HT [31], reversed the detrimental effects of high-temperature stress on egg-laying activity. However, immunizing against VIP had no effect on heat stress-induced decline in reproductive performance. This was despite the findings that both PCPA and antibodies to VIP attenuated the rise in circulating PRL, the increase in nesting frequency, and the expression of incubation behavior. The mechanism(s) underlying the differential effects of PCPA and VIP on heat-induced suppression of egg-laying activity are far from clear. The results of earlier studies from our laboratory have suggested that hyperprolactinemia associated with heat stress might be a causative factor in the reduced reproductive efficiency [32], as the antigonadotropic effects of PRL are well documented. PRL decreases reproductive activity by acting on the hypothalamus and inhibiting gonadotropin-releasing hormone release [32–34], on the pituitary to reduce LH-β subunit mRNA expression and LH release [35], and directly on the ovary, reducing steroidogenic enzyme mRNA expression, thus inhibiting steroid hormone production [36]. Elevated PRL levels have been shown to reduce photoinduced LH release and delay the onset of sexual maturity [37].

In agreement with the results of previous studies, the present study showed that VIP immunoneutralization lowered circulating PRL levels and prevented the induction of incubation behavior [27, 28]. However, unlike the previous studies, which were conducted in a thermoneutral environment [27, 38], VIP immunoneutralization did not maintain the egg-laying activity of turkey hens subjected to high temperature stress (Figs. 1A, 4B).

Taken together, these findings suggest that heat-induced hyperprolactinemia may not be the primary cause for the suppression in reproductive performance of heat-stressed female turkeys. Treatment with PCPA, an inhibitor of the rate-limiting enzyme in 5-HT pathway, lowered circulating PRL levels throughout the turkey reproductive cycle and maintained the egg-laying activity of heat-stressed birds. This is consistent with the antigonadotropic and PRL-stimulating effect of 5-HT. Treatment with PCPA results in the resumption of ovulatory cycles in hyperprolactinemic incubating turkeys [39] and accelerates photoinduced gonadal development [26]. Serotonin is a potent stimulator of avian

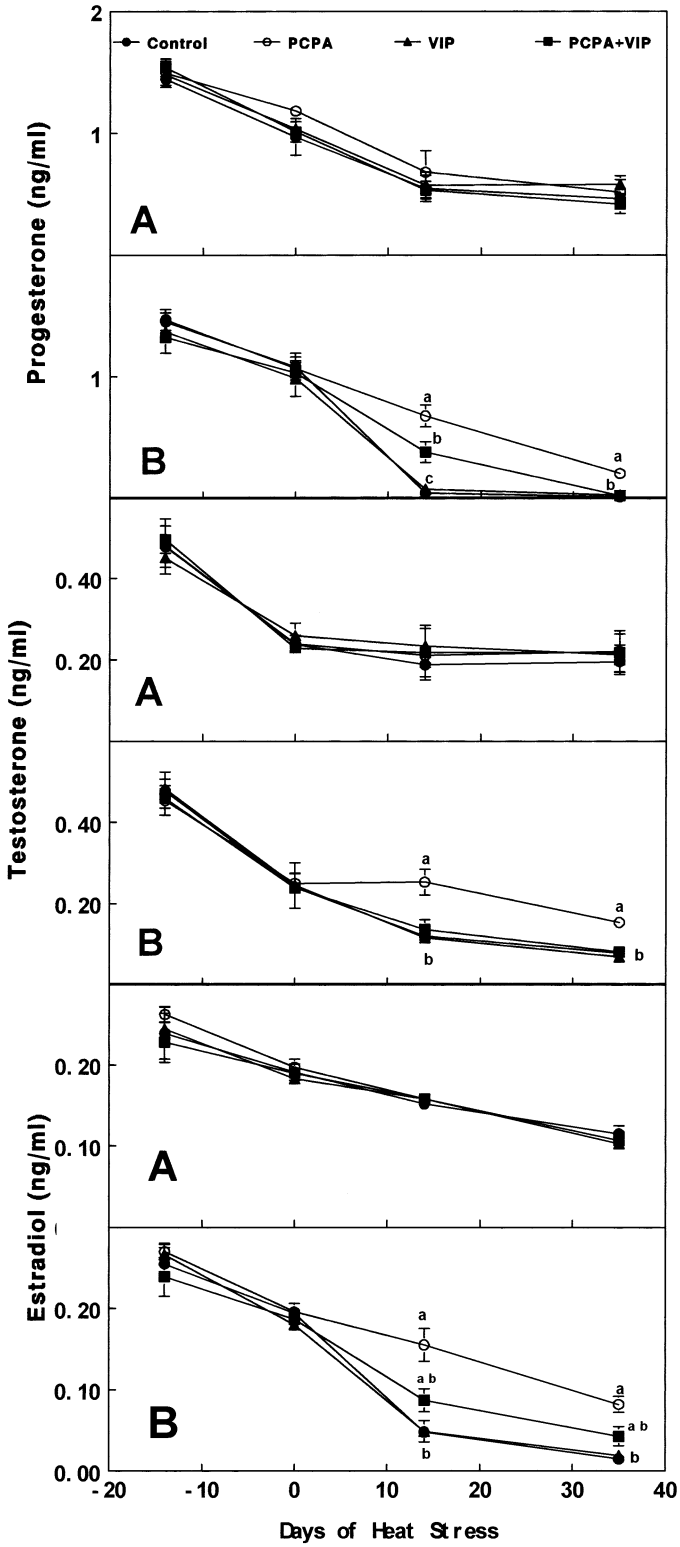

FIG. 6. Plasma progesterone, testosterone, estradiol of large, white female turkeys exposed to high environmental temperature (**A**) or maintained under thermoneutral conditions (**B**). Birds were treated with PCPA (PCPA), were actively immunized against VIP (VIP), received a combination of PCPA and active immunization against VIP (PCPA+VIP), or were untreated (control). Data are presented as mean ± SEM. Values indicated with different letters on the same day are significantly different ($P < 0.05$).

PRL secretion [40, 41] by acting at a central level, as 5-HT has no direct effect on the pituitary [42, 43]. Serotonin affects PRL secretion via a pathway that includes dopamine and VIP as the final mediator [44, 45]. It appears that the PRL-lowering effects of PCPA are mediated by the interference with the VIP-releasing mechanism(s).

The finding that treatment with PCPA maintained egg-laying activity in heat-stressed birds, which may be independent of its PRL-lowering effect, suggests an additional mechanism(s) by which PCPA reverses the detrimental effects of heat stress on the reproductive system. Indeed, 5-HT has been shown to be involved in the induction of hyperthermia [46], which is reduced by pretreatment with 5-HT receptor antagonists, specifically, the 5-HT_{2A} receptor subtype [47, 48]. It is suggested that the impairment of the ability to dissipate heat during exposure to heat stress is likely to contribute to the decline in reproductive performance and the treatment with PCPA depletes central 5-HT, thus reducing heat-induced hyperthermia and its detrimental effects on egg laying.

It is of interest to point out that, when PCPA was given to VIP-immunized turkeys, its effectiveness in maintaining egg production in heat-stressed turkeys declined dramatically. These findings are difficult to explain at this time. Additional studies are needed to clarify such an observation.

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