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EFFECT OF ACTH ON CORTICOSTEROID AND PROGESTERONE LEVELS IN FEMALE BABOONS DEPENDING ON THE PHASE OF THE MENSTRUAL CYCLE

T. N. Todua, N. P. Goncharov, G. V. Katsiya, V. I. Vorontsov, and B. A. Lapin

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KEY WORDS: hamadryad baboons; menstrual cycle; ACTH; progesterone; corticosteroids.

Dependence of adrenal secretion of glucocorticoids on ACTH has now been well studied. However, there is no unambiguous answer to the question of how the sensitivity of the adrenals to ACTH changes in relation to changes in sex hormone concentration in the peripheral blood. We know that the ACTH level in women changes in the course of the menstrual cycle [6]. Removal of the ovaries in rats leads to a decrease in synthesis of ACTH and its release from the pituitary [4]. An increase in adrenocortical activity in rats in the period of proestrus [11] and a preovulatory rise of the cortisol concentration in the peripheral blood of women have been discovered [6]. There is also evidence of a decrease in the trophic effect of ACTH in women after ovariectomy and its restoration by preliminary estrogen therapy [12].

To study the effect of ACTH on the endocrine function of steroid-producing glands depending on the level of sex hormones in the body, a comparative study of the dynamics of steroid hormones in the follicular and luteal phases of the menstrual cycle in response to a standard dose of ACTH was undertaken in experiments on hamadryad baboons.

EXPERIMENTAL METHOD

Five mature female hamadryad baboons weighing 12-21 kg and aged 8-13 years were used. The experimental animals had a regular menstrual cycle lasting 28-38 days. The state of the sex cycle of the baboons was monitored by observing swelling of the genital skin. The first day of menstrual bleeding was taken as the beginning of the cycle. Synthetic ACTH (B 1-24, ACTH, Synacthen) was injected intravenously in a dose of 1 U/kg body weight in the follicular (6th-9th days) and luteal phases of the cycle (21st-23rd day), during the period of maximal activity of the corpus luteus. Blood was taken from the cubital vein (8-10 ml) before and 30 min and 1, 2, 4, 24, and 48 h after injection of the ACTH. The plasma was obtained by centrifugation at 3000 rpm for 20 min and was kept at −20°C until required for assay. Concentrations of corticosterone, 11-deoxycortisol, and progesterone were determined in duplicate samples of plasma by radioimmunoassay [7]. Antisera obtained by the Laboratory of Experimental Endocrinology, Research Institute of Experimental Pathology and Therapy, Academy of Medical Sciences of the USSR, Sukhumi (TU 42.14, 333-82, 334-82, and 331-82) were used for determination. Cortisol (S) was determined by the competitive binding method [10]. Calibration curves were plotted between logit-log coordinates, and the steroid levels in the plasma were determined and the results subjected to statistical analysis by Student's t test on the "Élektronika 15-VSM-5" computer.

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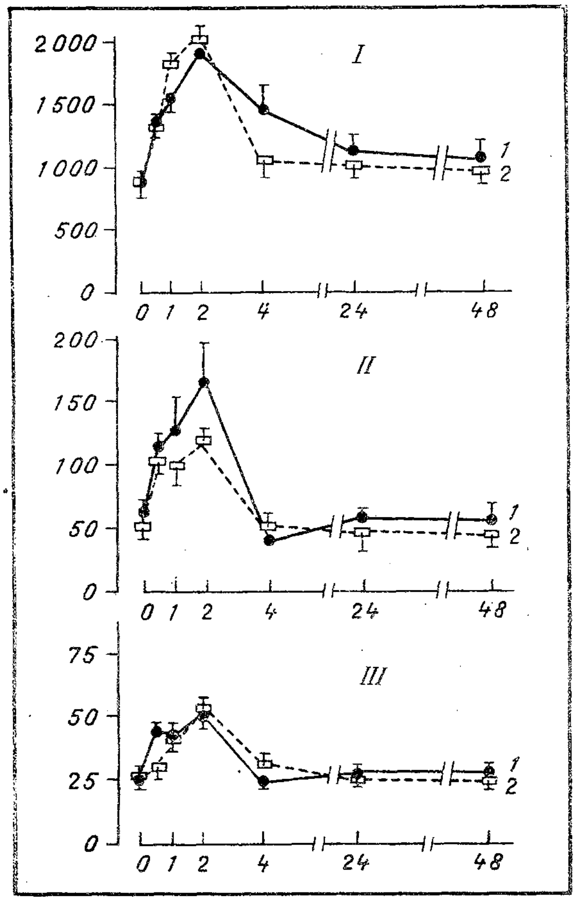

Fig. 1. Dynamics of peripheral blood corticosteroid levels in female hamadryad baboons after injections of ACTH (M±m). Abscissa, time (in h); ordinate, corticosteroid level (in nanomoles/liter). I) Cortisol; II) corticosterone; III) 11-deoxycortisol. Circles indicate follicular phase, rectangles – luteal phase of menstrual cycle.

EXPERIMENTAL RESULTS

Results of determination of the cortisol concentration in the peripheral blood of the baboons in response to injection of ACTH in the follicular and luteal phases of the menstrual cycle are given in Fig. 1. The peripheral blood cortisol concentration was significantly increased 30 min after injection of ACTH. The maximal increase in cortisol concentration was observed 2 h after injection of ACTH, namely 110–122% in both phases of the cycle. After 4 h the increase amounted to 66% in the follicular phase and 18% in the luteal phase of the cycle, followed by a gradual fall to the original level after 48 h. The dynamics of the response of corticosterone and 11-deoxycortisol correlated highly with the dynamics of the cortisol concentration in both phases of the cycle (in the follicular phase $r = 0.74$ and 0.89, in the luteal phase of the menstrual cycle $r = 0.91$ and 0.94 respectively). The maximal rise in the level of steroid hormones was recorded 2 h after injection of ACTH, and reached values of 155% ($P < 0.05$) and 130% ($P < 0.05$) respectively for corticosterone and 11-deoxycortisol in the follicular phase, and 141% ($P < 0.01$) in the luteal phase. Injection of exogenous ACTH into female hamadryad baboons thus led to marked activation of the glucocorticoid function of the adrenal cortex, and the degree of stimulation, under these circumstances, was independent of the phase of the menstrual cycle.

The dynamics of the changes in peripheral blood progesterone levels after injection of ACTH in different phases of the menstrual cycle is shown in Fig. 2. The progesterone concentration fell in all the animals in the luteal phase of the cycle. After 2 h the hormone level fell below its initial value by 32% ($P < 0.05$), and after 48 h the fall was 18%. In the follicular phase of the menstrual cycle a very small rise of the progesterone concentration was observed 2 h after injections of ACTH; it correlated with the dynamics of the cortisol level

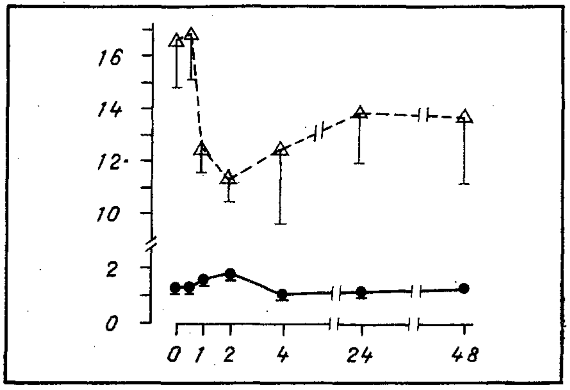

Fig. 2. Dynamics of peripheral blood progesterone concentration in female hamadryad baboons in response to injection of ACTH (M±m). Abscissa, time (in h); ordinate, progesterone level (in nanomoles/liter). Circles indicate follicular phase, triangles – luteal phase or menstrual cycle.

(r = 0.67). A study of the dynamics of steroid hormones in the female baboons during the 24-h period revealed a high degree of correlation between the circadian rhythms of cortisol and progesterone in the follicular phase of the cycle [1, 9]. These data suggested that the predominant source of progesterone in the formation of the peripheral pool in the follicular phase of female baboons is the adrenals.

The maximal increase in the blood cortisol concentration in the two phases of the cycle was recorded 2 h after injection of the hormone, and the small difference observed in the cortisol concentration 4 h after injection was not significant, and was evidently due to the lower mean steroid concentration during the 24-h period in the luteal phase of the cycle [1]. No difference were found in the character of the adrenal response to a single exposure of female baboons [8] and of women [3] to stress in different phases of the menstrual cycle.

The character of changes in the progesterone concentration in response to injection of ACTH, by contrast with that of glucocorticoids was determined by the phase of the menstrual cycle. For instance, in the luteal phase of the cycle injection of ACTH caused a significant lowering of the progesterone level from 16.7 and 11.3 nanomoles/liter. The progesterone concentration in the follicular phase was a little raised, and this correlated with the dynamics of the cortisol level. In the present experiments, in animals studied in the follicular phase of the cycle, the same adrenal character of the progesterone dynamics was observed. This suggests that in this case circadian fluctuations of the progesterone level were recorded, and not a specific response of the adrenals to injection of ACTH, more especially because a single exposure of females of this species to acute stress was not accompanied by any change in the progesterone level of adrenal origin [8]. Injection of exogenous ACTH in the luteal phase of the cycle disturbed the circadian rhythm of progesterone abruptly, causing a significant fall in the level of the hormone 2 h after injection. Release of endogenous ACTH caused similar depression of the progesterone level in female baboons, stressed in the luteal phase of the menstrual cycle. The fall in the progesterone level thus observed was due to the inhibitory effect of ACTH on secretory activity of the ovaries themselves, for the metabolic clearance of progesterone is unchanged throughout the duration of the menstrual cycle in baboons of a different species (Papio papio) and also in man after injection of exogenous ACTH [2, 5].

Consequently, the sensitivity of the adrenals to a single injection of ACTH is independent of the phase of the menstrual cycle and the inhibitory effects of ACTH on progesterone secretion is exhibited only in the presence of an actively functioning corpus luteus of the ovary.

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SEASONAL RHYTHMS OF INDOLEAMINE LEVELS IN THE RAT PINEAL GLAND

L. A. Bondarenko UDC 612.826.33.018

KEY WORDS: pineal gland; serotonin; melatonin; biological rhythms.

The role of the pineal gland in the manifestation of biological rhythms is generally familiar. It receives information mainly from the outside world and is an intermediary in interaction between organism and environment, thus enabling the living organism to orient itself to the alternation of day and night and to adapt itself in time. We know that the intensity of serotonin (5-HT) metabolism in pineal cells and formation of its hydroxylated and methoxylated derivatives depend on the intensity of illumination. Data in the literature are evidence that during the dark period of the year (just as during the dark time of the 24-h period) melatonin (MT) production in the pineal gland increases, whereas during the light period of the year (24-h period) it decreases [6, 8, 10] 10]. The opposite data were obtained for 5-HT [4, 12, 14].

Meanwhile the question of the content of other indoleamines in the pineal gland depending on the season has not been adequately discussed in the literature, and it was accordingly decided to study metabolic pathways of 5-HT and concentrations of individual indoleamine fractions in the pineal gland in summer and winter.

EXPERIMENTAL METHOD

Experiments were carried out on 48 mature male Wistar rats weighing 150-200 g. The rats were kept in the animal house under natural conditions of alternation of day and night. The experiments were undertaken at different times of year, with different conditions of daylight: in winter (8 h of daylight and 16 h of darkness) and in summer (16 h of daylight and 8 h of darkness). Levels of the following substances were determined in the pineal gland [12]: 5-HT, N-acetylserotonin (N-AS), MT, 5-methoxytryptamine (5-MOT), and total fractions of 5-hydroxyindoleacetic and 5-methoxyindoleacetic acids (5-HIAA and 5-metOIAA). The animals were decapitated at night (between 1 and 3 a.m., at the time of greatest activity of the pineal gland) in red light. Pineal glands from two or three animals were pooled for indoleamine determination. Fluorescence of the test substances was measured on a BIAN fluorometer at wavelengths of 365 and 470 nm. Weight parameters of the pineal were determined at the same time.

EXPERIMENTAL RESULTS

The results showed that the weight of the pineal gland is not constant but varies with the season of the year. In winter, for instance, the weight of the pineal glands of the rats was 1.61 ± 0.12 mg, whereas in summer it was 1.1 ± 0.08 mg ($P < 0.01$). Parameters of relative weight of the pineal glands showed similar changes.

The results of the biochemical investigation showed (Fig. 1) that the concentrations of 5-HT, N-AS, and MT in the pineal glands of the rats in winter were virtually identical. In summer, however, when the longest period of daylight is observed, the N-AS and MT levels fell abruptly and parallel with one another ($P < 0.001$), whereas the 5-HT concentration in the pineal gland was increased at this time of the year ($P < 0.01$). A different picture was observed when the concentration of 5-MOT was studied, for it increased parallel with the

Laboratory of Biochemistry of Endocrine Diseases, Khar'kov Research Institute of Endocrinology and Hormone Chemistry. (Presented by Academician of the Academy of Medical Sciences of the USSR L. T. Malaya.)
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