CHANGES IN PERIPHERAL BLOOD LEVELS OF STEROID HORMONES AND THEIR PRECURSORS IN *Papio hamadryas* UNDER STRESS

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The character of changes in the level of 12 steroids in peripheral blood plasma of male baboons (*Papio hamadryas*) under conditions of immobilization and surgical stress was determined by a radioimmunological method. During stress the concentration of androgens in the blood plasma of the monkeys is reduced, whereas the concentration of precursors of the steroid hormones and of hydrocortisone is increased. These changes are opposite in phase to the diurnal rhythm of the steroids. The fall in the levels of testosterone and dihydrotestosterone and the rise in the concentrations of pregnenolone, 17α-hydroxypregnenolone, and 17α-hydroxyprogesterone in the blood plasma of male baboons exposed to stress were found to be the most objective and sensitive criteria of the stressor situation.

KEY WORDS: steroids; peripheral blood; stress; *Papio hamadryas*.

The important role of corticosteroids of the hydrocortisone type in responses of the animal to stressor situations is now generally accepted. At the same time, little is known about the hormonal function of the gonads in extremal situations or of the character of correlation in the changes in the levels of the steroid hormones and their precursors. Most of the data on hormonal reactions in stress have been obtained in experiments on small laboratory animals which, in the character of their steroid secretion and metabolism, differ significantly from man [3, 9, 10].

The baboon *Papio hamadryas*, in which the character of steroid secretion and metabolism is very similar to that in man [1, 8] was chosen as the experimental model with which to study possible changes in the balance of hydrocortisone, androgens, gestagens, estrogens, and their precursors during stress.

EXPERIMENTAL METHOD

Experiments were carried out on eight sexually mature male baboons aged 8-12 years. Stress was induced in five animals by immobilizing them in the supine position for 2 h. Blood was taken 10 h before immobilization, 30 min and 1, 2, 3, 4, and 6 h after the beginning of immobilization, and again 24, 48, and 72 h later. The character of the change in the peripheral blood steroid concentration was studied in three baboons during surgical stress (the operation of cannulation of the adrenal and testicular veins under barbiturate anesthesia).

The steroid concentration was determined in two parallel samples of plasma by a radioimmunological method [4, 6], adapted for monkey plasma [5, 7]. The following steroids were determined simultaneously in the same sample of plasma: progesterone, pregnenolone, 17α-hydroxyprogesterone, 20α-dihydroprogesterone, 17α-hydroxypregnenolone, estrone, estradiol, dehydroepiandrosterone, androstenedione, testosterone, and 5α-dihydrotestosterone.

Hydrocortisone was determined by the competitive binding method [11]. The standard curve was plotted, the steroid concentration in the plasma samples calculated, and the statistical analysis of the results carried out by means of the Élektronika 15-VSM-5 computer, using specially designed programs.

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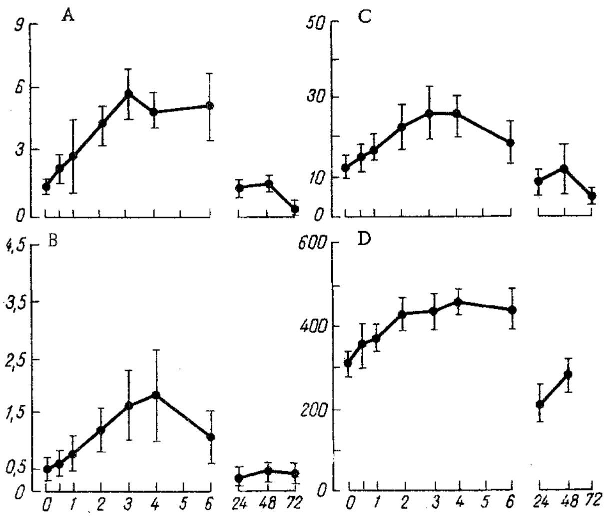

Fig. 1. Dynamics of concentration of hydrocortisone and steroid precursors in plasma of immobilized monkeys. A) Pregnenolone; B) 17α-hydroxyprogesterone; C) 17α-hydroxypregnenolone; D) hydrocortisone. Here and in Figs. 2 and 3: abscissa, time after action of stressor (in h); ordinate, hormone concentration (in ng/ml).

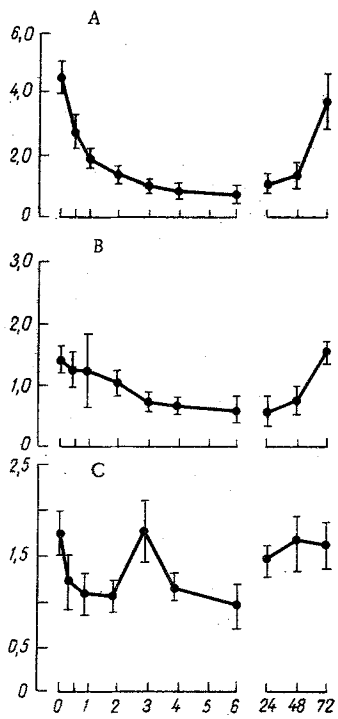

Fig. 2. Effect of immobilization stress on androgen concentration in peripheral blood of P. hamadryas. A) Testosterone, B) 5α-dihydrotestosterone; C) androstenedione.

TABLE 1. Effect of Surgical Stress on Peripheral Blood Plasma Steroid Concentrations in P. hamadryas (in pg/ml; M ± m)

Time of investigation and number of animals	Progesterone	Pregnenolone	17α-hydroxyprogesterone	20α-dihydroprogesterone	17α-hydroxypregnenolone	Estrone	Estradiol	Dehydroepiandrosterone	Androstenedione	Testosterone	5α-dihydrotestosterone	Hydrocortisone
Before operation	373,5	829,5	396,7	289,0	8 785,0	52,4	20,1	7 814,0	777,3	6 290.1	2 326,2	324
(n=24)	±11,2	±137,8	±39,7	±26,6	±706,4	±3,4	±1,5	±830	±63,5	±724,3	±141,4	±21,5
1-2 h after operation	447,8	6 107,8	990,3	664,8	72 687,7	33,4	30,9	32 054.3	3 734,7	1 388.9	1 669,2	742,8
(n=9)	±35,8	±1 704	±174,5	±53,9	±20 807,0	±5.5	±1,8	±8 440	±499,3	±171,5	±198,7	±81,4
P	<0,02	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	<0,01	<0,001

Legend. Hydrocortisone concentration given in ng/ml.

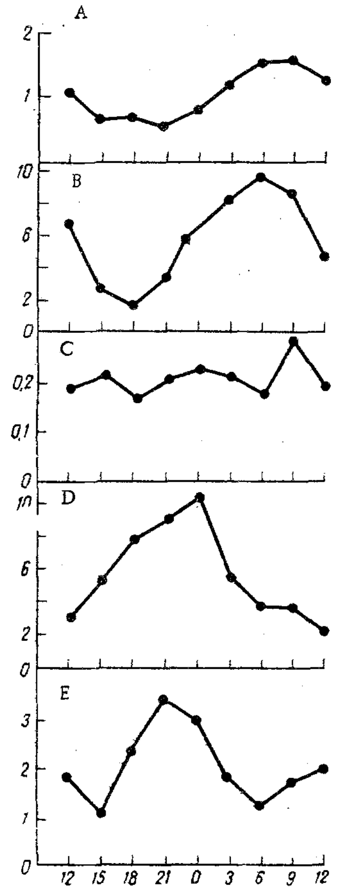

Fig. 3. Diurnal rhythms of plasma steroid levels in monkeys: A) pregnenolone; B) 17α-hydroxypregnenolone; C) 17α-hydroxyprogesterone; D) testosterone; E) 5α-dihydrotestosterone.

EXPERIMENTAL RESULTS

Since a radioimmunological method enabling the concentrations of the steroid sex hormones and their precursors to be determined simultaneously was used, it was possible to study not only the character of the change in the steroid levels in different stressor situations, but also to assess to some extent the direction of steroidogenesis in the adrenals and testes.

Curves showing changes in the levels of hydrocortisone and three of its precursors (pregnenolone, 17α-hydroxypregnenolone, and 17α-hydroxyprogesterone) during immobilization stress are given in Fig. 1. They show that the concentration of precursors in the plasma increased from 2 to 5 times to reach a maximum 3-4 h after the beginning (i.e., 1-2 h after the end) of immobilization. The concentration of progesterone and its metabolite (20α-dihydroprogesterone) in the blood of the monkeys in a state of stress was unchanged. The character of the curve reflecting the dynamics of hydrocortisone in stress was similar with the type of the curves reflecting the dynamics of its precursors. However, the increase in the hydrocortisone level did not exceed 70-80%. The change in the concentration of the above-mentioned steroids in the plasma reflects principally the process of steroidogenesis in the adrenals, for in baboons these steroids are secreted mainly by the adrenals [2]. The absence of change in the progesterone concentration during stress suggests that the increase in the intensity of hydrocortisone formation in this case takes place via the Δ^5-pregnenolone → 17α-hydroxypregnenolone → 17α-hydroxyprogesterone pathway and not via the Δ^4-pregnenolone → progesterone → 17α-hydroxyprogesterone pathway.

The concentration of estrogens (estradiol and estrone) in the blood plasma of the male baboons was virtually unchanged during the action of the stressor. By contrast with hydrocortisone and its precursors, the blood concentration of the androgens showed considerable changes (Fig. 2). The testosterone level, which fell by 60% in the course of immobilization of the animals for 2 h, proved to be the most sensitive index. It continued to fall during the next 4 h also, when the males were back in their usual situation. The decrease in the blood testosterone concentration still continued 48 h after the end of exposure to the stressor. The dynamics of the plasma dihydrotestosterone concentration of the monkeys exposed to stress repeated the dynamics of testosterone, although quantitatively speaking the changes were less severe.

The blood concentration of androstenedione during stress fell by almost half during immobilization, after which its level rose a little and then fell again below its initial value. The androgen level was restored 2-3 days after exposure to stress. In one of the experimental baboons the initial plasma testosterone level was low (800 pg/ml). In this case immobilization was not accompanied by a fall in the testosterone level. The inhibitory effect of stress on androgen production was evidently manifested against the background of an active functional state of the pituitary–gonads system. The change in the concentration of dehydroepiandrosterone in response to stress differed in different monkeys: in two animals it increased from 1074 to 14,174 pg/ml, whereas in the rest it remained unchanged.

The study of the dynamics of the steroid concentration on the day of exposure to stress continued from 10 a.m. to 4 p.m., and for that reason when the results were analyzed it was necessary to study physiological fluctuations in the steroid level associated with the diurnal rhythm.

The diurnal rhythms of those steroids which showed the greatest changes during stress were studied in five intact baboons (Fig. 3). The lowest concentrations of pregnenolone, 17α-hydroxypregnenolone, and 17α-hydroxyprogesterone were observed between 3 and 6 p.m., whereas the blood testosterone and 5α-dihydrotestosterone concentrations were increased during this period. It can be concluded from the character of the curves in Fig. 3, and also of those in Figs. 1 and 2, that changes in the steroid levels during stress are not due to their diurnal rhythms but are in fact opposite in phase to them. Consequently, exposure to the stressor leads to a disturbance of the diurnal rhythms of the blood plasma steroid concentrations.

The next essential step was to assess the degree of specificity of the hormonal response to the stressor. For this purpose the same spectrum of steroids as above was studied in male baboons during surgical stress. These experiments (Table 1) showed that the pregnenolone, 17α-hydroxypregnenolone, and 17α-hydroxyprogesterone levels in the peripheral blood plasma of the monkeys increased by 7, 8, and 3 times respectively. During surgical stress an increase was observed also in the concentration of progesterone and, in particular, of its metabolite 20α-dihydroprogesterone. The plasma estrogen concentration in this case changed in opposite directions: the estrone level fell whereas the estradiol level rose. The androgen balance was substantially changed. The blood testosterone concentration was reduced by 78%, whereas the levels of its precursors (dehydroepiandrosterone and androstenedione) rose sharply.

Unlike immobilization stress, surgical stress was accompanied by a marked rise in the plasma hydrocortisone level.

Hence, regardless of the character of the stressor, the hormonal response of the male baboons took the form of elevation of the blood levels of hydrocortisone and precursors of the steroid hormones and a fall in the concentration of androgens (testosterone and 5α-dihydrotestosterone). However, during surgical stress these changes were much more marked and affected the Δ^4 pathway of steroid synthesis as well as the process of estrogen formation.

During evaluation of stressor reactions in males, changes in the blood levels of precursors of the steroid hormones and androgens are the most sensitive and objective criterion.

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EFFECT OF PERIOD OF ADAPTATION ON THE COURSE OF EXPERIMENTAL HEART FAILURE AT HIGH ALTITUDES IN THE MOUNTAINS

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Data on the state of compensatory hyperfunction of the circulation and respiration in animals with varied degrees of mitral incompetence are given in relation to the periods of adaptation to high-altitude hypoxia in the mountains. In unadapted animals with mitral incompetence more severe disturbances of the hemodynamics and gas exchange were found, accompanied by congestion in the pulmonary and systemic circulatory systems. During the first day after formation of the lesion 52.9% of the animals died. In animals adapted to high-altitude hypoxia the disturbances of the circulation and respiration were milder and only 28.6% of the animals died.

KEY WORDS: adaptation; mitral incompetence; compensatory hyperfunction.

Despite many clinical and experimental studies of circulatory failure, few such investigations have been undertaken under high mountain conditions. Most of these observations have been made in cases of combined, decompensated cardiac defects [5, 7, 9, 11]. Under the climatic conditions of the Tyan'-Shan' Mountains valvular disease of the heart accounts for a high proportion of diseases of the cardiovascular system [1, 6]. According to the statistics [2], about 70% of all valvular lesions of the heart affect the mitral valve.

Hence the urgency of the study of the functions of the cardiovascular and respiratory systems in animals with mitral incompetence under extremal mountain conditions.

The object of this investigation was to study the degree of compensatory hyperfunction of the heart developing after measured resection of the mitral valve in animals depending on the periods of stay in the mountains and to determine any special features of the course of heart failure under the conditions of high-altitude hypoxia.

EXPERIMENTAL METHOD

Experiments were carried out on mongrel dogs of both sexes weighing 17-30 kg. In the experiments of series I (17 dogs) mitral incompetence was produced by surgical operation on the 2nd-4th day after the ascent from the city of Frunze (760 m above sea level) to the Tuya-Ashu Pass (3200 m above sea level). In series II (14 dogs) mitral incompetence was produced after preliminary adaptation for 60 days to an altitude of 3200 m above sea level. Measured mitral incompetence (10-15% of the total area) was produced by the method suggested by Chechulin and Bobkov [10]. Function tests were carried out on the animals before and for 30-60 days after the operation. The gas exchange was determined by the open method, hemodynamic indices by the dye method in the writer's modification for chronic experiments [4], and the venous pressure in the lesser saphenous vein in the leg was measured by Waldman's apparatus. Phase analysis of left ventricular systole was carried out by acceleration kinetocardiography [8], with synchronous recording of the ECG by the Élkar apparatus. The calculations and statistical analysis of the results were carried out by the Iskra-112 and Mir-1 computers.

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