DYNAMICS OF BLOOD LEVELS OF ALDOSTERONE AND OF CORTISOL AND ITS PRECURSORS IN Macaca rhesus DURING PROLONGED HYPOKINESIA

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Changes in the external environment are known to cause marked disturbances of the activity of all organs and systems of the body. Adaptation to new conditions is produced by neural and humoral mechanisms. A special role in adaptation processes is played by the adrenals, which produce glucocorticoids, which have been called adaptive hormones. Reactions of the adrenals to various types of short-term procedures have been the subject of many investigations [1, 8]. However, few data have been obtained on the state of the hypophyseo-adrenal system in long-term extremal situations [4, 5]. In the last few years interest has sharply increased in changes arising under the influence of the factors of space flight and, in particular, those connected with a decrease in the volume and strength of muscular activity. Limitation of motor activity with the body in the horizontal position, known as clinostatic hypokinesia, is a widely used model of this state. Data on the hormonal status obtained on small laboratory animals, which differ considerably from man in the spectrum of the steroids they produce, cannot always be extrapolated to man. The adequate study of adrenal function is possible only on primates – the animals closest to man as regards synthesis, secretion, and metabolism of steroid hormones.

This paper gives the results of an investigation of the dynamics of the concentration of aldosterone and of cortisol and its precursors in the blood plasma of Macaca rhesus during prolonged limitation of motor activity.

EXPERIMENTAL METHOD

Experiments were carried out on five sexually mature male rhesus monkeys weighing 6-10 kg. The animal's motor activity was limited by individual constraining combination suits, secured to lodgments, in the form of a frame, with a tarpaulin tightly stretched over it. Immobilization in this way enabled movements of the trunk, hind limbs, and, to some extent, of the head to be prevented while permitting free movement of the forelimbs. The duration of the test period of hypokinesia was 17 days. Blood samples were taken immediately before and 1, 3 and 6 h and 1, 2, 3, 7, 10, and 17 days after immobilization. The diet throughout the period of the investigation was of constant composition and included bread, cottage cheese, fruit, and vegetables.

Blood in a volume of 5 ml was taken from the cubital vein. Plasma was separated by centrifugation and frozen and kept at −20°C until steroids in it were determined.

Cortisol was determined by the method of competitive binding with protein [14] and 11-deoxycortisol was determined by radioimmunologic assay in 20 μl of plasma. The high specificity of the antiserum for aldosterone enabled the determination to be carried out in 100 μl plasma without chromatographic fractionation. The parallelism test was used as the criterion of reliability of aldosterone determination (the coefficient of parallelism was 0.17 and the permissible value was up to 4.9). Radioimmunologic reactions for 11-deoxycortisol and aldosterone were carried out in a manner similar to those described previously for other steroids [2]. 17-Hydroxyprogesterone (17-Δ^4-P) and 17-hydroxypregnenolone (17-Δ^5-P) were determined by a radioimmunologic method after fractionation on columns with Celite [2].

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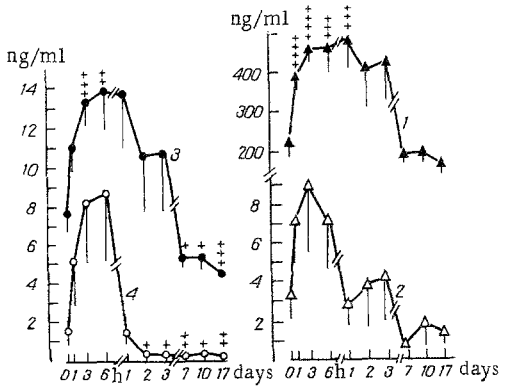

Fig. 1. Dynamics of plasma concentrations of cortisol and its precursors during hypokinesia. 1) Cortisol; 2) 17-hydroxypregnenolone; 3) 11-deoxycortisol; 4) 17-hydroxyprogesterone. ++++ $P < 0.001$, +++ $P < 0.01$, ++ $P < 0.02$, + $P < 0.05$ – degree of significance of differences compared with initial level. Abscissa, time of investigation; ordinate, concentration of steroid in plasma (in ng/ml).

Calculation of the standard curves and steroid concentrations and statistical analysis of the results were carried out on an "Elektronika-15 VSM 5" computer by programs specially compiled for it.

EXPERIMENTAL RESULTS

As Fig. 1 shows, the initial period of hypokinesia was characterized by a rapid and considerable rise of the blood cortisol concentration. Its peak level was observed 3-6 h after the beginning of recording, and was 86% higher than the basal level. Maximal concentrations of 11-deoxycortisol, 17-Δ^4-P, and 17-Δ^5-P were observed at these same times, and were 83, 545, and 445% respectively higher than the initial values. These results are evidence that hypokinesia is a powerful stressor factor for M. rhesus. The similarity of the dynamics of the plasma levels of cortisol, 11-deoxycortisol, 17-Δ^4-P, and 17-Δ^5-P during the first 6 h of the experiment is consistent with data showing that the hormone and its precursors respond in a similar manner to acute stress in lower primates [8].

However, during the next three days of hypokinesia considerable differences were observed in the reaction of these compounds. Whereas the concentration of cortisol remained close to the peak level, the concentrations of 11-deoxycortisol and, in particular, of 17-Δ^4-P and 17-Δ^5-P fell sharply to their initial values or below on the second or third day. A similar dynamics of these steroids was observed by other workers in men during prolonged administration of ACTH [7, 11]. Characteristically this picture was observed only during chronic, but not acute, stimulation of the adrenals by ACTH. Changes in the ratio of cortisol to its precursors are evidently connected with the direct stimulating effect of ACTH on activity of enzymes concerned in the late stages of corticosteroid synthesis [11].

The results suggest that the fall in the concentrations of 11-deoxycortisol, 17-Δ^4-P, and 17-Δ^5-P in the blood of monkeys is due to prolonged and intensive production of ACTH and that it reflects a reorganization of the activity of the glands toward the fuller utilization of intermediates in the process of synthesis of the adaptive hormone – hydrocortisone.

On the 7th-17th days of hypokinesia, the content of all the steroids studied in the plasma was below its initial value. The concentrations of cortisol, 11-deoxycortisol, 17-Δ^4-P, and 17-Δ^5-P toward the end of the experiment were 77, 62, 39, and 15% respectively of their initial values. These results agree with data showing a fall in the corticosteroid concentrations in the plasma [4-6] and adrenals [4] of laboratory animals and man during restriction of motor activity.

The decrease in secretory activity of the adrenals during hypokinesia is evidently adaptive in character. The reduction of the total flow of sensory information ultimately leads to the establishment of a new and more

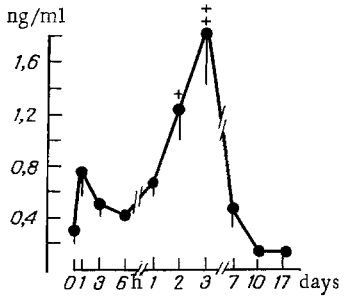

Fig. 2. Dynamics of plasma aldosterone concentration during hypokinesia. ++ $P < 0.002$, + $P < 0.01$). Degree of significance of differences from initial level. Abscissa, time of investigation; ordinate, aldosterone concentration (in ng/ml).

economical level of function of the hypophyseal-adrenal system, corresponding to the reduced demands of the body for hormonal influences from the adrenals. This hypothesis is in agreement with data showing a decrease in the plasma ACTH concentration in rats during prolonged fixation [4].

The decrease in the concentrations of cortisol precursors discovered during the chronic period of hypokinesia is thus evidently connected with reduced stimulation of adrenal steroid synthesis by ACTH. The fact that the concentration of cortisol itself was not reduced so considerably can be explained by delay in the catabolism of this most important glucocorticoid in muscle tissue during physical rest [1]. A decrease in its transformation in the liver under clinostatic conditions likewise cannot be ruled out.

As Fig. 2 shows, the blood aldosterone concentration was increased as early as 1 h after the beginning of the experiment. However, its dynamics during the first 6 h of hypokinesia did not correlate with the dynamics of cortisol. The absence of correlation between the levels of these hormones in the plasma also was observed during administration of ACTH in man [13]; it is evidently connected with differences in the sensitivity of the zona fasciculata and zona glomerulosa to ACTH [12]. The maximal increase in the blood aldosterone concentration of monkeys was observed on the second or third day of the experiment. On the basis of data in the literature showing increased excretion of sodium in the initial stages of simulated weightlessness [3], it is suggested that in the present investigation the dynamics of the aldosterone concentration reflects changes in water and mineral metabolism. Later, on the 10th-17th day, its concentration was considerably reduced. A fall in the level of this mineralocorticoid in the plasma has been found in man during repeated hypokinesia [10]. This dynamics is evidently connected with the well-known phenomenon that much less aldosterone is secreted in recumbency than in the sitting or standing position [9].

Contradictions between the results of the present investigation and those obtained by other workers, who found an increase in the aldosterone concentrations during clinostatic hypokinesia, are difficult to discuss without a parallel study of the whole complex of factors participating in the regulation of the production of this hormone [5].

On the basis of the results of this investigation it is thus possible to distinguish two stages in the response of the adrenals of M. rhesus to prolonged limitation of motor activity: a stage of sustained activity lasting from 3 to 6 days and a stage of adaptation with the establishment of a new, relatively low level of adrenal functional activity, to correspond to the reduced environmental demands. The dynamics of the concentration of aldosterone, the principal mineralocorticoid hormone, evidently reflects changes in water and mineral metabolism during clinostatic hypokinesia.

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PHAGOCYTIC AND LYMPHOID CELLS IN TISSUE REACTIONS TO ASEPTIC INFLAMMATION

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A previous investigation [1] showed that injury to macrophages, polymorphonuclear leukocytes (polymorphs), and lymphocytes initiates the development of inflammatory changes. The object of the present investigation was to study the connection between the state of these cells and the character of tissue inflammatory changes with special reference to aseptic inflammation.

EXPERIMENTAL METHOD

A sterile nylon thread 0.7 mm in diameter and 15 cm long was introduced into the peritoneal cavity of 20 rabbits. The development of inflammation was studied 3 days, 2 weeks, and 2 and 4 months later (in five animals at each time). Twelve healthy rabbits served as the control.

Squash preparations from the peritoneal cavity and trachea and blood films were stained with hematoxylin–eosin. Deoxyribonucleoproteins (DNP, by Feulgen's method), ribonucleoproteins (RNP, by Brachet's method), total protein (by mercuric chloride and bromphenol blue), and activity of NAD-diaphorase (with nitro-BT) and acid phosphatase (by Burstone's method) were determined in them. Squash preparations from the peritoneal cavity also were stained by Gram's method. In films stained with hematoxylin and eosin the cell composition in per cent was calculated and the number of destroyed cells counted. When films in which acid phosphatase was found were assessed, activity of the enzyme was determined and the permeability of the lysosomal membranes was estimated from the number of cells with a diffuse type of distribution of the reaction product [2]. In each of 600 films at least 100 cells were assessed by means of a point system, and the mean cytochemical index (MCI) was calculated and the results subjected to statistical analysis to determine significant differences by Student's t-test ($n < 30$). Tissue of the capsule formed around the foreign body in the peritoneal cavity and lung tissue were investigated histologically.

EXPERIMENTAL RESULTS

The development of aseptic (confirmed by bacterioscopy) intraperitoneal inflammation after introduction of the foreign body was accompanied by three stages of changes in the macrophages, polymorphs, and lympho-

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