

L. A. Shitov and A. A. Viru

UDC 612.453.018+612.433.451.018]-  
06:612.766.1

KEY WORDS: ACTH; cortisol; physical work.

Activation of the hypophyseo-adrenocortical system under the influence of stressors takes place mainly by a neurogenic mechanism involving hypothalamic and other limbic structures of the CNS [1, 4, 6]. At the same time there is evidence that modulations of the response may arise through feedback from peripheral blood glucocorticoid and ACTH levels [12, 13]. A high initial blood glucocorticoid [8, 10] or ACTH [14] level, and also previous administration of dexamethasone [15], depress activation of the hypophyseo-adrenocortical system (HACS) during physical exertion. Meanwhile in adrenalectomized patients (with Cushing's disease) elevation of the blood ACTH level was more marked during work than in normal healthy individuals [7].

For further investigation of the role of feedback in the regulation of function of the HACS, it was decided to study relations between ACTH and cortisol during and after static work in dogs under normal conditions and after pharmacologic inhibition of glucocorticoid secretion.

## EXPERIMENTAL METHOD

Experiments were carried out on nine mature mongrel male dogs weighing 18-25 kg. The effect of two types of static work was studied: 1) moderate work consisting of carrying on the back a load equal to 40% of the maximally tolerable load for 30 min, and 2) heavy work - carrying a load on the back equal to 60% of the maximally tolerable load. Venous blood was taken before work, during work (at the 3rd, 5th, 10th, 30th, and 60th minutes), and after work (15, 30, 45, and 60 min later). The serum concentration of ACTH and cortisol were determined by radioimmunoassay using test kits from CIS (France and Italy) and IMOO PHASE (USA).

The experiments were repeated after long-term administration of cloditan (dichloro-diphenyltrichloroethane), which inhibits glucocorticoid secretion by the adrenals [3]. Cloditan was given *per os* after meals in a dose of 0.1 g/kg daily for 1.5 months.

## EXPERIMENTAL RESULTS

Under the influence of static work, activity of the HACS increased rapidly. At the 3rd minute of load carrying, judging by ACTH secretion, a twofold response of the pituitary was observed in the dogs. In some animals the ACTH level fell, in others it rose. As a result, no significant changes in the plasma ACTH level could be found when either load was carried. By the 5th minute moderate work the blood ACTH level was increased by 46% (Fig. 1), whereas during heavy work it was increased by 168% (Fig. 2); the cortisol level was increased by 36 and 61% respectively. By the 10th minute the ACTH level was even higher, and was 67% above the initial level during moderate work and 283% higher during heavy work. The cortisol concentration subsequently increased only during moderate work, and by the 10th minute its level reached the values observed at the 5th minute during heavy work. The blood ACTH level subsequently fell. At the 30th minute it was lower than initially during both heavy and moderate work. Meanwhile the cortisol level remained high during heavy work but showed a tendency to fall during moderate work. During the last 30 min of heavy work the blood ACTH level rose again, and at the end of work it was twice as high as initially; the cortisol concentration, however, was maintained at the level which it reached by the 5th minute of work. After the

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Department of Physiology, Brest Pedagogic Institute. Department of Sport Physiology, Tartu University. (Presented by Academician of the Academy of Medical Sciences of the USSR P. D. Gorizontov.) Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 98, No. 10, pp. 391-393, October, 1984. Original article submitted August 30, 1983.

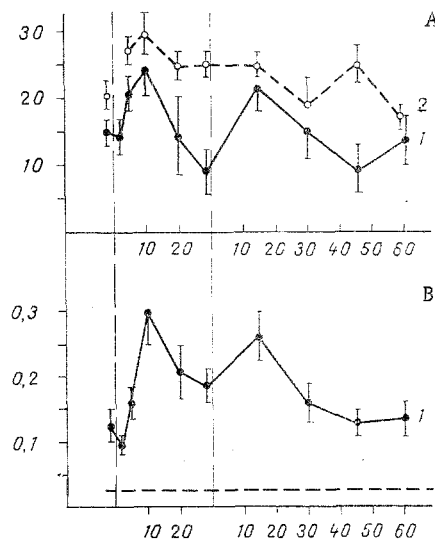


Fig. 1. Changes in plasma ACTH (A) and cortisol (B) levels in dogs during moderate static work. Abscissa, time (in min); ordinate, ACTH (in pg/ml) and cortisol (in μg/ml) concentration. 1) Normal, 2) chlodian.

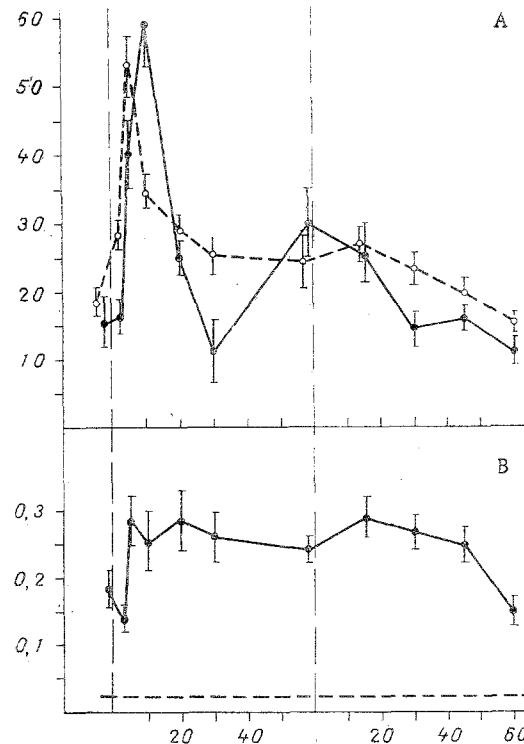


Fig. 2. Changes in plasma ACTH (A) and cortisol (B) levels in dogs during heavy static work. Legend as to Fig. 1.

end of moderate work the ACTH level rose significantly, which was not observed after more prolonged heavy work. In both cases the cortisol level rose a little during the first 15 min after work, but this was followed by a fall in the blood levels of both ACTH and cortisol. In both cases the ACTH concentration fell below its initial value (45 min after moderate and 60-90 min after heavy work). The plasma cortisol concentration as a rule returned to its initial level 30 min after moderate work and 60 min after heavy work.

After long-term administration of chlodian no cortisol was found in the blood serum either at rest or during work. Under these conditions the blood ACTH level rose rather faster than in the control dogs (Figs. 1 and 2). However, the maximal level achieved at the 5th or 10th minutes did not differ from the maximal level under normal conditions. In the absence

of cortisol in the blood, the ACTH concentration fell sharply toward the 10th minute of heavy work, and thereafter it continued to fall more steadily. However, its level was higher than initially. It maintained this level until the end of work of both categories, and during the first 30 min of the recovery period after heavy work. The ACTH concentration was significantly higher than initially at the 15th and 45th minutes of rest after moderate work.

These results obtained on dogs agree with rapid activation of the HACS observed in man during work [10]. An increase in the blood glucocorticoid concentration during the first 10 min of static work also was observed by Pegel' et al. [5] in young dogs. Immediately after this they found that the 11-hydroxycorticoid concentration returned to its initial value despite continuation of static work. Our own observations revealed a decrease in the ACTH concentration to or even below its initial level during work of both categories, and also a decrease in the cortisol concentration during moderate work at the 30th minute also. During heavy work the cortisol level remained high until the end of work.

During heavy work a significant difference was thus found in the time course of the ACTH and cortisol levels. During static work by man a transient wave of an increase in the blood ACTH level also was observed and was combined with a more prolonged rise of the blood cortisol level [10]. This reflects the principle that the duration of action of the regulating hormone is shorter than the response of the regulated hormone [2].

Comparison of the initial activation of the HACS during work of the two categories also revealed differences in the changes in ACTH and cortisol concentrations in the blood. Whereas an increase in the load was accompanied by an increase in both the intensity and the degree of the rise in the blood ACTH concentration, with regard to the changes in cortisol the picture was different. During heavy work the cortisol concentration rose more rapidly but by a lesser degree, and by contrast with the effect of moderate work, the high blood cortisol level was maintained until the end of work. The stronger response of the blood ACTH level was thus reflected only in longer maintenance of the high blood cortisol level. Experiments *in vitro* showed a biphasic increase in glucocorticoid biosynthesis by the adrenals in response to ACTH: an initial rapid, followed by a prolonged increase in biosynthesis [11]. Activation of the phase of prolonged increase of corticosteroid biosynthesis *in vivo* probable requires a greater increase in the blood ACTH concentration.

The period of high intensity of pituitary corticotrophic function a short time after the beginning of work may be attributed to the inhibitory action of elevation of the blood cortisol level by a feedback mechanism. Experiments on dogs in which glucocorticoid secretion was abolished by preliminary administration of chlodian showed that even here the blood ACTH concentration fell after an initial rise. However, the fall was less marked than normally, and the raised blood ACTH level was subsequently maintained. Cessation of the period of high intensity of the pituitary corticotrophic function is thus not due to the action of the raised blood glucocorticoid level, although the degree of temporary inhibition of corticotrophic function depends on the feedback effect of the raised blood cortisol level. The results also indicate that in the absence of cortisol in the blood, activation of corticotrophic function proceeds more rapidly at the beginning of work than when the blood cortisol concentration before work was normal.

The small rise in the blood cortisol level during the first 15 min after work may be linked either with secondary intensification of the corticotrophic reaction (function) observed immediately after moderate work and until the end of heavy work or with a decrease in the rate of elimination of cortisol from the blood, which was demonstrated after a period of dynamic work lasting 60 min [9].

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