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EFFECT OF FEVER ON REACTIVITY OF THE ADRENAL CORTEX

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When introduced into the body, bacterial pyrogens are known to activate the pituitary-adrenal system [1-3, 5-7]. However, this fact cannot be regarded as undisputed proof of the interdependence of pyrexial and glucocorticoid reactions, for fever, if produced by leukocytic pyrogen, freed to some degree from balanced substances, and a more adequate stimulus for the organism, is not accompanied by the hormonal response described above [3]. These and other data are evidence that activation of the adrenal cortex in response to administration of bacterial pyrogens and also of native (unpurified) leukocytic pyrogen is unconnected with elevation of the body temperature. The absence of any strict parallel between the pyrexial reaction and the response of the pituitary-adrenal system also indicates that the mechanisms triggering them are relatively independent. Nevertheless, this does not rule out the possibility that a febrile reaction may affect the functional state and reactivity of the adrenal cortex. The study of this problem is of great interest from both theoretical and practical points of view, if the clinical use of pyrogenic agents is taken into account.

The object of this investigation was to study the effect of fever on the reactivity of the adrenal cortex following administration of its natural stimulator, adrenocorticotrophic hormone (ACTH).

EXPERIMENTAL METHOD

Male rabbits were used. The reaction of the adrenal cortex was assessed by measuring changes in the 11-hydroxycorticosteroid (11-HCS) concentration in peripheral blood plasma by the method of Usvatova and Pankov [4] in response to intravenous injection of ACTH. Pyrogenal or leukocytic pyrogen (both native and after partial alcoholic purification – the low-molecular-weight specific pyrogenically active fraction) were used as pyrogens. Pyrogenal was injected intravenously in a dose of two minimal pyrogenic doses (MPD) per kg and leukocytic pyrogen also was injected intravenously (at once or by the drip method) in a dose of 1.5 ml/kg. For intravenous drop injection of leukocytic pyrogen at the rate of 1 ml/h, a polyethylene catheter was fixed in the rabbit's auricular vein. Pyrogen-free physiological saline was injected into control animals under similar conditions. The rectal temperature was measured at a depth of 4 cm by means of a fixed transducer connected to an electrothermometer, every 30 min during the first 2 h of the experiment, and subsequently every hour. The results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

In the experiments of series I, one-stage intravenous injection of pyrogenal or of native leukocytic pyrogen was used as the pyrogenic agents. The animals developed the ordinary febrile reaction [3], accompanied by elevation of the 11-HCS level on average by 67.1% (pyrogenal) and 57.2% (native leukocytic pyrogen). Injection of ACTH against the background of fever induced by pyrogenal (in the stage of fever and an already

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raised 11-HCS level) led to a small (on average by 14.4%), transient, additional increase, not statistically significant, in the plasma corticosterone concentration (initial level 11.9 μg%, 17.4 ± 1.67 μg% 45 min after injection of pyrogenal, and 19.9 ± 2.16 μg% 30 min after injection of ACTH preceded by pyrogenal; $P > 0.05$). Similar changes in the plasma 11-HCS concentration also were observed in the experiments with native leukocytic pyrogen (initial level 11.7 μg%, rising to 18.4 ± 1.5 μg% 45 min after injection of leukocytic pyrogen, and to 21.8 ± 2.7 μg% 30 min after injection of ACTH preceded by native leukocytic pyrogen; $P < 0.05$). In the control experiments, injection of ACTH did not affect the body temperature, but led to a greater increase (on average by 50.4%) in the plasma 11-HCS concentration: from 12.5 ± 0.8 to 15.7 ± 1.6 μg % after 30 min ($P < 0.05$), to 18.1 ± 3.1 μg% after 90 min ($P < 0.05$), and to 18.8 ± 2.05 μg % after 150 min ($P < 0.05$).

The physiological saline used in the control experiments had no effect either on body temperature or on adrenocortical activity.

In the experiments of series II the febrile reaction in the rabbits was induced by prolonged intravenous drop injection of the low-molecular-weight pyrogenically active fraction of leukocytic pyrogen, with a febrile reaction lasting 4-7 h. Despite the marked febrile reaction in this case, the plasma 11-HCS level remained unchanged. Injection of ACTH against this background led to results which differed depending on how long after the beginning of fever the ACTH was given. When ACTH was injected into the animals 2 h after the beginning of intravenous drip injection of purified leukocytic pyrogen, from an initial plasma 11-HCS concentration of 10.4 ± 0.82 μg% it increased by 102% (21.1 ± 0.79 μg%; $P < 0.05$) 30 min, by 74% (18.1 ± 0.76 μg%; $P < 0.05$) 90 min, and 21.1% (12.6 ± 2.99 μg%; $P < 0.05$) 210 min after injection of ACTH. In the same experiments, when ACTH was injected 5 h after the experimental animals had developed fever, the increase in the 11-HCS concentration from its initial level (before ACTH) of 7.1 ± 1.4 μg% was much less: 69% (12.0 ± 1.1 μg%; $P < 0.05$) 30 min, and 29% (9.2 ± 1.03 μg%; $P < 0.05$) 90 min after injection of ACTH, whereas 210 min after ACTH the 11-HCS level was lower than initially (6.9 ± 0.79 μg%; $P < 0.05$).

Meanwhile, in control experiments in which physiological saline was injected, also by the intravenous drip method, instead of pyrogen, injection of ACTH (2 h after the beginning of drip injection) gave the following increase in the plasma 11-HCS from its initial value of 8.06 ± 1.15 μg%: 128.3% (18.4 ± 0.43 μg ; $P < 0.05$) after 30 min, 139.4% (19.3 ± 0.42 μg%; $P < 0.05$) after 90 min, 70% (13.7 ± 2.18 μg%; $P < 0.05$) after 150 min, and 27.8% (10.3 ± 1.74 μg%; $P > 0.05$) after 210 min.

The results can be summarized in the statement that ACTH, when administered in the presence of increased glucocorticoid activity as a result of pyrogenal or native leukocytic pyrogen, causes only a slight and transient additional increase, not statistically significant, in the 11-HCS concentration. This depression of the reaction might be explained by the considerable preliminary activation of the adrenal cortex by the pyrogens mentioned above. However, in the other series of experiments with intravenous drip injection of the low-molecular-weight fraction of leukocytic pyrogen, when the plasma 11-HCS level remained unchanged throughout the febrile period, the glucocorticoid response to ACTH nevertheless remained low compared with the control, and the degree to which it was depressed depended on the duration of the fever. It can be concluded from these results that the reactivity of the adrenal cortex is depressed during fever.

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