Adaptive Effects of Dexamethasone in Stress Exposure

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Disorders in the compensatory adaptive processes underlie the development of many somatic diseases. The neuroimmunoendocrine complex and one of its main components, the hypothalamic—pituitary—adrenal system, play the leading role in the maintenance of the adaptation reserve. Treatment with a synthetic analog of hydrocortisone (final effector of this system) in low doses modulates its function by inducing positive changes in the adaptive mechanisms under conditions of stress exposure.

Key Words: *adaptation; hydrocortisone; adrenocorticotropic hormone; insulin; dexamethasone*

Failure of the compensatory adaptive reactions is a component of the genesis of a pathological process [1-5,10,12]. Adequate therapy should be not only etiotropic and pathogenetically justified, but should also contain elements increasing natural resistance and, which is important, creating conditions for restoration of reserves for compensation of the stress aftereffects.

The hypothalamic—pituitary—adrenal cortex system plays the leading role in mechanisms of nonspecific reactivity; its functional activity is regulated by very intricate feedback contours [2-4,6-9,11].

Corticosteroids dose-dependently inhibit hormone production by the hypothalamic—pituitary—adrenal system. These effects of systemic glucocorticoids underlie the concept of regulation of body resistance by low-dose glucocorticoids, for example, dexamethasone (DM; a synthetic analog of hydrocortisone). Due to pharmacokinetic and pharmacodynamic characteristics of DM, a constant minimum daily concentration of the synthetic hormone can be created without development of side effects of steroid therapy.

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We studied the possibility of limiting the stress stimulation during treatment with low-dose DM.

MATERIALS AND METHODS

The study was carried out on 10 healthy volunteers (men aged 25-40 years; mean age 31.2±2.7 years) without allergic reactions or diseases. All participants gave written informed consent to participation in the study. The volunteers did not participate in clinical studies within 30 days before our study, had no alcohol and drug abuse, used no drugs of any kind for 2 weeks before the study. The volunteers were hospitalized at the clinic of Institute of Pharmacology. Their status was evaluated by the following parameters: case history, physical examination, common and biochemical blood tests, urine analysis, electrocardiography, and blood pressure measurements.

On the day of the study the cubital vein was cannulated (I. V. Catheter Size 20G) and 15 ml blood was collected at 8.00 for evaluating the basal biochemical parameters and hormones (ACTH, hydrocortisone, and insulin). Blood hormones were then measured at certain periods over 24 h. After installation of the catheter (after 1.5 h) the patients received a standard breakfast. The catheter was removed from the vein after the 12th blood collection (after 24 h) and an aseptic dressing was

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applied. The study was repeated according to the same protocol after 7 days; the patients received 0.5 mg DM at 8.00 after overnight fasting.

The hormonal status was evaluated on a COBAS-CORE complete automated enzyme immunoassay analyzer. Serum hydrocortisone, insulin, and ACTH were measured twice daily according to manufacturer's instructions (DSL, Inc. and Alcok Bio).

The results were statistically processed using Statistica 6.0 software.

RESULTS

No side effects, allergic reactions, or DM intolerance were detected during the study.

Twenty-four-hour monitoring of insulin, ACTH, and hydrocortisone concentrations gave new data on their intracircadian deviations. Changes in the concentrations of these hormones indicated that the morning increment in hydrocortisone level lagged behind that of ACTH (Fig. 1). This phenomenon could be detected only after analysis of individual data because of great differences in hormone concentrations and small sampling. The procedure of intravasal catheter installation (at 8.00) for blood collection was regarded as an element of stress exposure, which was reflected in the 24-h curves of hormone incretion. Changes in ACTH concentration were most pronounced; its physiological peak, normally observed at 7.50-8.00, was shifted to 9.00 and reached 94.3±4.2 pg/ml. The maximum concentration of hydrocortisone was also observed during this period, this indicating the incorrectness of using discrete information, which does not permit evaluating the regulatory effect of ACTH on hydrocortisone production. Moderate hydrocortisone stimulation, detected at 16.00-20.00, with the peak at 18.00 (316±27 nmol/liter) also did not help detect the anticipating stimulatory increment in ACTH concentration. It seems to be due to the impossibility of detecting this phenomenon by collecting blood samples at 2-h intervals. The mutual regulation relationships were most clearly seen in analysis of blood samples collected at 6.00 and 8.00, when elevation of ACTH level was paralleled by a pronounced increment in hydrocortisone concentration (to 351.7±22.1 nmol/liter).

Following up the circadian changes in insulin concentration, we hoped to detect their relationship with the levels of hydrocortisone as a counter-hormone, at least within the framework of their stress-realizing and stress-limiting effects. However, a moderate decrease in insulin level was observed in response to installation of intravasal catheter, when hydrocortisone concentration increased. Presumably, these opposite changes in the concentrations of hormones have nothing to do with the reaction to stress (because of its minimum degree) and should be regarded as the natural rhythms of secretion, at least for insulin. Further elevation of insulin concentrations (at 10.00 and 14.00; 12.2±1.3 and 9.8±1.2 mU/liter, respectively) was most likely due to meals. Only the increase in its concentration at 20.00 somewhat lagged behind the meals; however, this very elevation of insulin concentration corresponded by its degree and by time to the increase in insulin secretion, recorded at 18.00.

Changes in the hormone levels were detected under conditions of reduced DM test as well. The level of ACTH recorded at 8.00 slightly increased by 9.00 (from 86.3±6.1 to 89.5±5.5 pg/ml; Fig. 1), presumably, because of the stressing effect of catheter installation procedure. However this increment was less pronounced in comparison with the control (94.3±4.2 pg/ml), which, judging by the drug pharmacokinetics, could be due to the inhibitory effect of DM. By 10.00 a pronounced ($p<0.05$) decrease in ACTH concentration in comparison with the control was recorded. Later the level of ACTH was statistically lower than in the control until 24.00. At 24.00 and 4.00 ACTH concentrations were minimum and in some cases could not be analyzed by the method used in the study. It is most likely that this fact was responsible for similarity of ACTH concentrations in the control and during DM test. No expected physiological and associated with the circadian rhythm increment of ACTH concentration in the morning (6.00-8.00) was observed after DM intake. However, judging by the results, the curve of ACTH concentrations under conditions of DM treatment became more flat.

The concentrations of hydrocortisone under conditions of DM test also differed significantly from the control. Despite a higher level of hydrocortisone at 8.00 in comparison with the control, the stress effect of intravasal catheter installation not only failed to lead to its elevation, but even caused its decrease from 427.0±33.7 to 411.0±27.0 nmol/liter. This can be explained by the extinguishing effects of the exogenous hormone. Later (at 10.00, 11.00, and 12.00) the most pronounced decrease in hydrocortisone concentration was recorded, with the minimum "plateau" at 174.0±6.5-269.0±11.1 nmol/liter. The circadian rhythm of hydrocortisone secretion is lost. Starting from 12.00 the deviations in the hormone concentration are minimum and are significantly less pronounced than in the control. Hence, a single dose of DM leads to significant changes in hydrocortisone incretion, somewhat elevating its basal level.

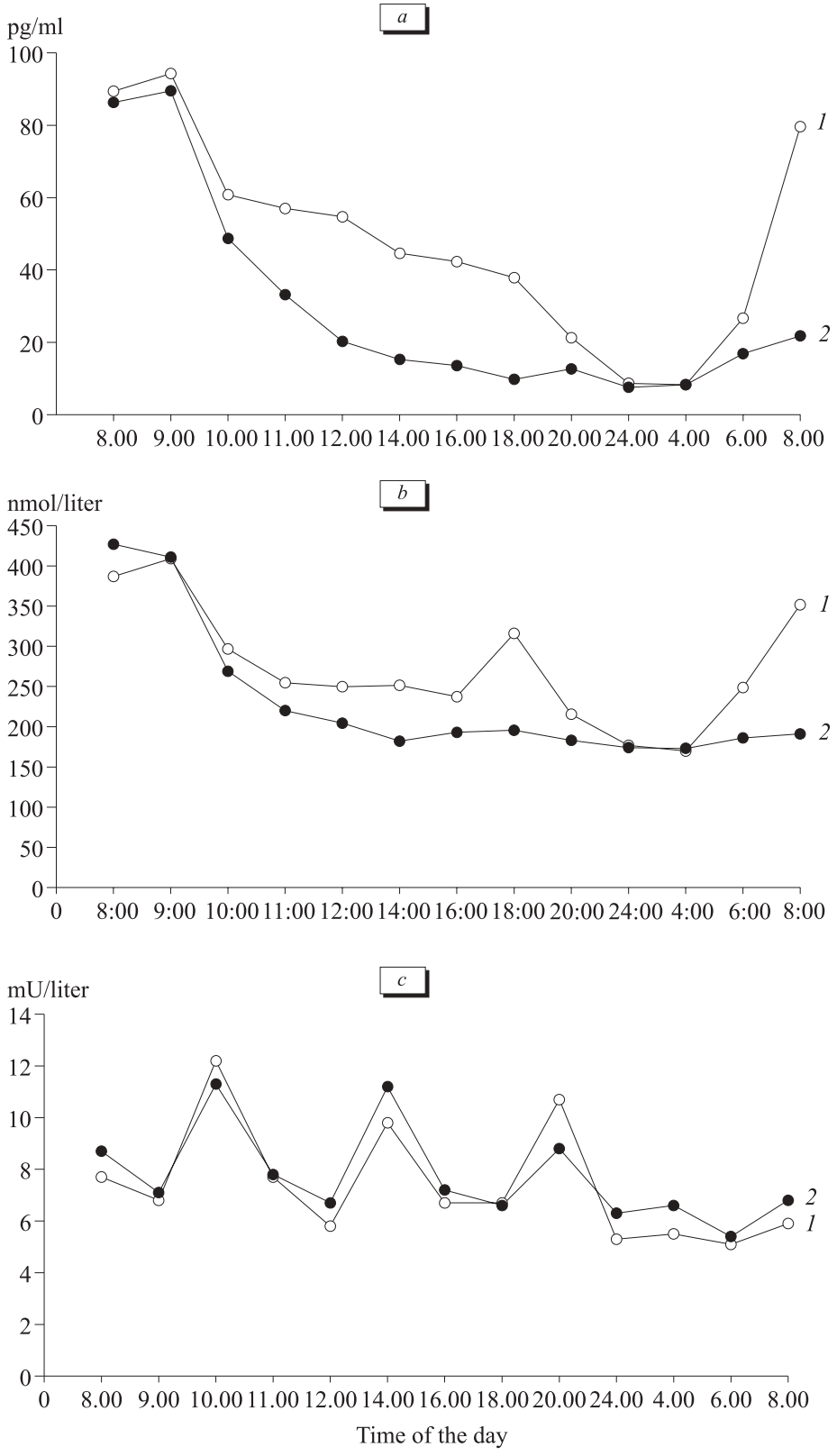

Fig. 1. Intracircadian changes in serum ACTH (*a*), hydrocortisone (*b*), and insulin (*c*) concentrations in normal subjects in the control (*1*) and under conditions of reduced DM test (*2*).

Insulin monitoring detected no relationship between this hormone and hydrocortisone levels in the control or under conditions of the test. However, in contrast to the control, the level of insulin moderately decreased in response to catheterization of the vein (when hydrocortisone concentration decreased, presumably under the effect of DM), and this insulin decrease being more pronounced due

to its initially high levels. Elevation of insulin concentrations at 10.00, 4.00, and 20.00 was determined (similarly as in the control) by meals. The increment of insulin concentration at 20.00, also delayed in comparison with the meals time, was less pronounced in comparison with the control (8.8±0.7 and 10.7±0.7 mU/liter in the control). No relationship between changes in insulin concentrations at 20.00, 24.00, and 4.00, 6.00, and 8.00 and hydrocortisone concentrations was detected. The absence of pronounced changes in ACTH and hydrocortisone concentrations in the morning hours was paralleled by an increase in insulin level. The most pronounced characteristic feature of insulin time course during the test were great differences between individual values, sometimes reaching 200% (in contrast to the control), the "monotony" of differences in the values inside the group not surpassing 50%.

Hence, a single dose of DM, due to its pharmacokinetic characteristics, led to long-term flattening of drops in the levels of "pulsatile" concentrations of serum hydrocortisone. In turn, these very "prolapses" of hydrocortisone concentration, reaching the critical level, directly activate the hypothalamic-pituitary-adrenal axis and, specifically, ACTH production. The 24-hour monitoring of hormones showed that a single dose of DM modified not only circadian rhythms of ACTH and hydrocortisone secretion, but modulated, presumably more intensely, their intracircadian fluctuations.

Changes in the time course of ACTH and hydrocortisone concentrations after DM intake evidence artificial modulation of their production rhythm. The resultant hydrocortisone "plateau" (at its lower mean values), virtually not changing during 24 h, and the elements of hydrocortisone-ACTH relationship suggest modulation, in other words, creation of a new level of the system's work. We mean here the changing levels of adaptive function of the two latter components of the hormonal hypothalamic-pituitary-adrenal axis. One more important factor, permanently present in the study, is (though not standard) stress effect of the procedures of preparation to blood collection (installation of the intravasal catheter), which once more confirms the efficiency of low-dose DM for limiting the stress reaction.

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