Content of Steroid Hormones in the Blood and Adrenal Glands of Mice in the Dynamics of BCG- and SiO_2-Induced Granulomatous Inflammation

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Individual or combined administration of BCG vaccine and silicon dioxide to male mice induced a nonspecific stress response of the adrenal glands and gonads judging from changes in the concentration of blood cortisol and testosterone. The dynamics of cortisol concentration in the adrenal glands was similar, while changes in progesterone concentration were in antiphase to those in the blood. After combined administration of both inductors of granulomatous inflammation, changes in the concentrations of the studied hormones to a greater extent corresponded to their dynamics after injection of BCG.

Key Words: *chronic granulomatous inflammation; BCG vaccine; silicon dioxide; corticosteroids; testosterone*

Activation of macrophages under the action of endogenous and exogenous factors and synthesis of primary mediators of inflammation involve into the biological reaction of inflammation not only immunocompetent cells, but also hypothalamic neurosecretory nuclei and hence modulate functional activity of the endocrine system [7,9]. Changes in the synthesis and secretion of glucocorticoids and their interrelations with inflammation mediators largely determine individual parameters of this pathological process.

Granulomatous process is a variant of chronic inflammation. The development of inflammation by the granulomatous variant can be realized irrespective on biological and physicochemical properties of its inductors (prokaryotes, eukaryotes, or non-biological factors) [3,8]. This attests to unspecific component in organism's response, which implies a peculiar character of the reaction of the regulatory systems of the organism, in particular, the endocrine system. Induction of chronic granulomatous inflammation (GI) by eukaryotes *C. albicans* fungi in CBA mice leads to hypocorticism, which was characterized by phasic course in the dynamics of candidiasis [6].

Here we studied the content of cortisol and testosterone in the blood and cortisol and progesterone in the adrenal glands (AG) of CBA mice in the dynamics of BCG- and SiO_2-induced inflammation, *i.e.* during induction of inflammation by prokaryotes and non-biological factors, and their combination.

MATERIALS AND METHODS

The study was performed on 200 male CBA mice obtained from Nursery of Institute of Cytology and Genetics, Siberian Division of Russian Academy of Sciences (Novosibirsk). The mice were divided into 4 groups. Group 1 mice received intravenous injection (into the caudal vein) of SiO_2 in 0.2 ml 0.9% isotonic aqueous solution of NaCl (100 μg/kg body

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weight). In group 2 animals, tuberculous GI was modeled by intraperitoneal administration of 0.5 mg BCG vaccine (Allergen) in 0.2 ml 0.9% isotonic aqueous solution of NaCl [2]. Group 3 mice received SiO_2 injection and after 10 day BCG vaccine in the above specified doses. Group 4 mice (controls) received 0.2 ml 0.9% isotonic aqueous solution of NaCl (intraperitoneally).

Animals of groups 1 and 2 were sacrificed 3, 10, 28, 56, and 120 days after injection of inflammation inductor, group 3 mice were killed at the same terms after injection of BCG vaccine. The concentrations of cortisol and testosterone in the blood and the content of cortisol and progesterone in AG were measured by radioimmune and enzyme immunoassays using Cortisol — RIA Immunotech, Testosterone EIA, and Progesterone EIA kits (Khema-Medica)

The data were processed statistically using Kruskal—Wallis dispersion analysis and nonparametric Mann—Whitney test (with the use of Bonferroni correction for multiple comparisons) [1]. The probability of validity of the null-hypothesis was accepted at 5% significance level.

RESULTS

The changes in blood content of cortisol in experimental mice were similar in the dynamics of BCG- and SiO_2-induced GI: the maximum was observed on day 10 and minimum of day 56 after infection of inflammation inductor (Fig. 1, *a*). The maximum increase in this hormone was noted in mice receiving SiO_2 (3-fold higher than in controls). On day 28, the concentration of cortisol in animals of all three experimental groups was 2-fold below the control. By the end of the experiment, blood cortisol content in group 1 mice returned to the control level, while in animals of groups 2 and 3 this parameter remained lowered (Fig. 1, *a*). Changes in blood cortisol concentration were similar in groups 2 and 3.

Thus, changes in cortisol concentration in the blood in the dynamics of chronic GI induced by BCG, SiO_2, or their combination have a nonspecific character similar to that observed during the action of various stress factors on the organism: initial increase in hormone concentration during the first days after inflammation induction is followed by its decrease and subsequent normalization of this parameter [5].

The dynamics of blood testosterone concentration in experimental animals was opposite to that of cortisol concentration (Fig. 1, *b*) with its minimum on day 10 and recovery of the control testosterone level on day 56 of the experiment in mice of groups 1 and 2. In mice of groups 2 and 3, the concentration of testosterone increased on day 3 after injection of the vaccine, but then decreased on day 10 (in group 3 this decrease was less pronounced than in group 2). After 28 days, the content of testosterone was equally low in all experimental groups, but in group 3 this parameter returned to the control level more slowly than in group 2.

In mice of all three experimental groups, the concentration of cortisol in AG decreased on day 3 after administration of GI inductors, while after 10 days this parameter returned to the control level (Fig. 2, *a*). Then, the content of cortisol in AG decreased again and attained its minimum on day 56;

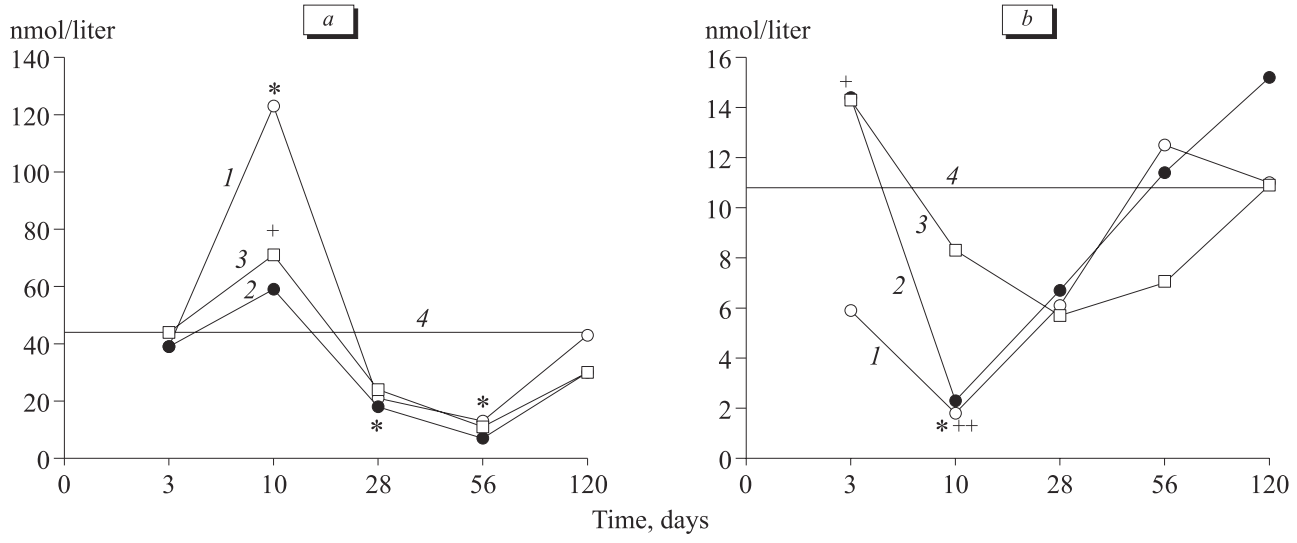

Fig. 1. Blood content of cortisol (*a*) and testosterone (*b*) in mice. Here and on Fig. 2: *1-4*: groups 1-4, respectively; $p<0.05$ compared to: *control, +group 1, °group 3.

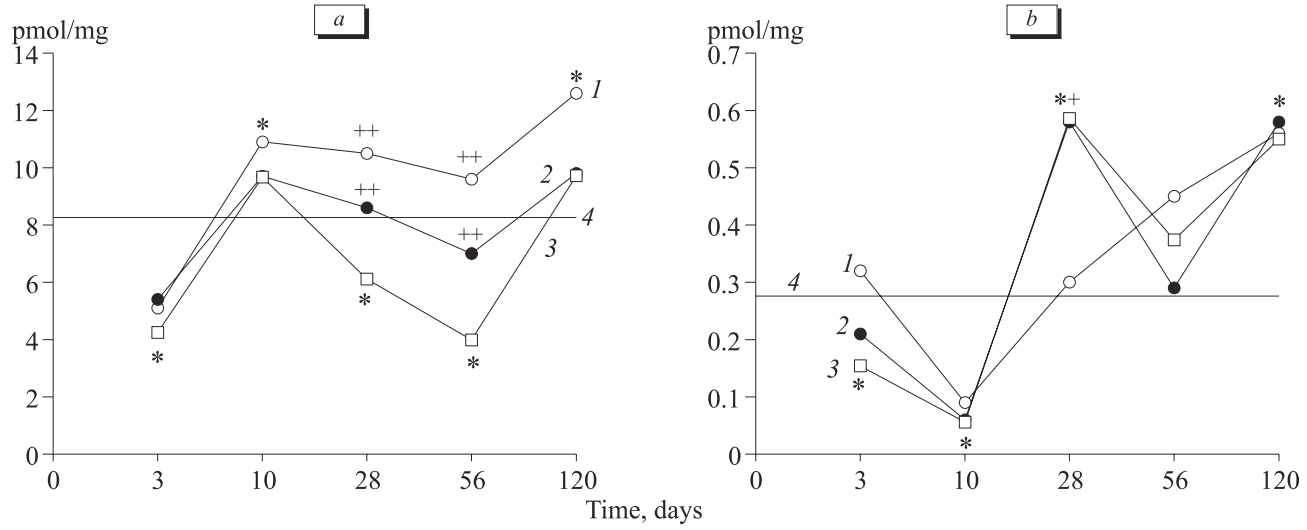

Fig. 2. Content of cortisol (*a*) and progesterone (*b*) in AG of mice.

this was followed by its recovery to the control values (groups 2 and 3) or above-control (group 1) values. Despite similar changes, the magnitude of fluctuations of the cortisol content was maximum after combined treatment with two inflammation inductors.

Changes in the progesterone content in AG in all experimental groups at the early terms of inflammation (days 3 and 10) can also be considered as a manifestation of stress response to administration of granulomagenic factors and GI development, because the decrease in this parameter on day 10 was observed against the background of increased cortisol content in the blood (Fig. 2, *b*). Then the content of progesterone in AG gradually increased in group 1 mice, while in mice of groups 2 and 3, this parameter decreased again on day 56 (similarly to the dynamics of cortisol content in AG), but on day 120 it 2-fold surpassed the control values. This increase in progesterone content attested to activation of steroidogenesis processes in AG.

Thus, the response of AG and gonads of male mice to individual or combined treatment with BCG vaccine and SiO_2 evaluated by blood concentrations of cortisol and testosterone and the content of cortisol and progesterone in AG differed from the reaction of these endocrine glands in CBA mice to *C. albicans* infection [4,6] and was characterized by a nonspecific pattern similar to the response to chronic stress factors exposure.

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