preparations, further research in this direction will make a definite contribution to the study of the immunomodulating effect of histamine and the mechanism of its action.

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SENSITIVITY TO MURINE TOXIN AND LEVEL OF MACROPHAGAL 5′-NUCLEOTIDASE ACTIVITY

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KEY WORDS: 5′-nucleotidase; macrophages; murine toxin of *Yersinia pestis*; salmosan

Murine toxin is a highly active lethal toxin of protein nature from *Yersinia estis* which is the principal component of fraction II of the plague microorganism. One of the principal points of application of the action of immunomodulators, and also of murine toxin, is the mononuclear phagocytic system (MPS) [1, 3].

In view of the foregoing remarks it was decided to study the effect of the immunomodulating preparation salmosan on sensitivity of mice to fraction II of *Yersinia pestis* and to determine the role of macrophages in this process.

EXPERIMENTAL METHOD

Experiments were carried out on male CBA mice weighing 16-18 g during the winter. The immunomodulator salmosan, of bacterial origin, was used. Salmosan was obtained in the Laboratory of Natural Immunity, N. F. Gamaleya Research Institute of Epidemiology and Microbiology, Academy of Medical Sciences of the USSR (M. A. Tumanyan, N. G. Sinilova, A. P. Duplisheva), and was injected subcutaneously and intraperitoneally in doses of 10 and 100 μg. Fraction II was injected intraperitoneally 1 or 7 days after injection of salmosan. Fraction II was isolated from *Y. pestis* strain NIIEG, grown at 37°C, by salting out from the filtrate of a broth culture at between 0.40 and 0.65 of saturation [5]. Any murine

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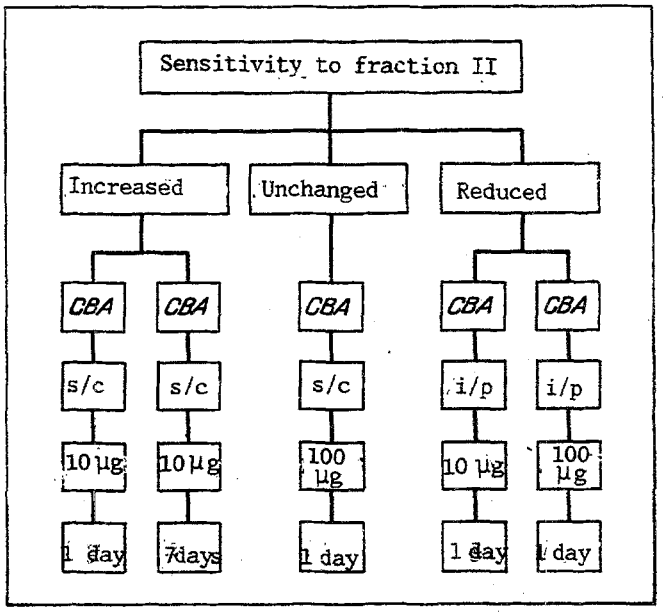

Fig. 1. Changes in sensitivity of CBA mice to fraction II of *Y. pestis* under the influence of the immunomodulator salmosan.

toxin present in it was identified by the immunodiffusion test in agar with antitoxic serum, generously provided by T. I. Domaradskaya. After isolation of fraction II, the state of the animals was kept under observation, noting the number which died, and on that basis, determining LD_{50} of the plague toxin. Animals of the control group received an injection of physiological saline followed by injection of the toxin in a similar manner. Changes in sensitivity to the toxin were determined by comparing LD_{50} in the control and experimental groups of mice. LD_{50} was calculated by the method in [4].

EXPERIMENTAL RESULTS

Analysis of the experimental results showed that the experiments as a whole can be divided into three groups depending on the sensitivity of the mice to the toxin, injected after salmosan (Fig. 1).

In the 1st group of experiments, under the influence of salmosan the mice showed an increase in sensitivity to the plague toxin. In these experiments, CBA mice were given a subcutaneous injection of salmosan in a dose of 10 mg 1 or 7 days before injection of the toxin.

In the 2nd group of experiments no change was observed in sensitivity to the toxin under the influence of salmosan. Sensitivity to the toxin was unchanged 1 day after subcutaneous injection of salmosan in a dose of 100 μg per mouse.

In the 3rd group of experiments, a decrease in the sensitivity of the mice to the toxin was observed after intraperitoneal injection of salmosan.

In other words, the investigation showed that, depending on the dose and mode of administration, salmosan had a varied action on the sensitivity of CBA mice to murine toxin.

It is well known that the character of action of the toxin on the animal is largely determined by the state of the MPS [3]. Numerous investigations also have demonstrated the important effect of immunomodulators, salmosan in particular, on various parameters of cells of the MPS [1]. Accordingly, in the next stage of the investigation an attempt was made to elucidate the role of macrophages in the change of sensitivity of mice to this toxin. For this purpose changes in certain biochemical and functional characteristics of PEM were analyzed under the influence of salmosan. The results showed a high degree of correlation between the change in sensitivity to the toxin and the level of activity of ecto 5′-nucleotidase in MPS. An increase in the sensitivity to the toxin was observed in cases when the immunomodulator led to increased activity of 5′-N in MPS. A decrease in the sensitivity to the toxin was observed in experiments in which salmosan caused a decrease in activity of the enzyme in MPS. When, however, the immunomodulator did not affect 5′-N activity, sensitivity to the toxin remained at the control level. The facts described above are illustrated by the planimetric construction of two-factor regression models describing dependence of 5′-N activity in MPS on the dose of salmosan and on the

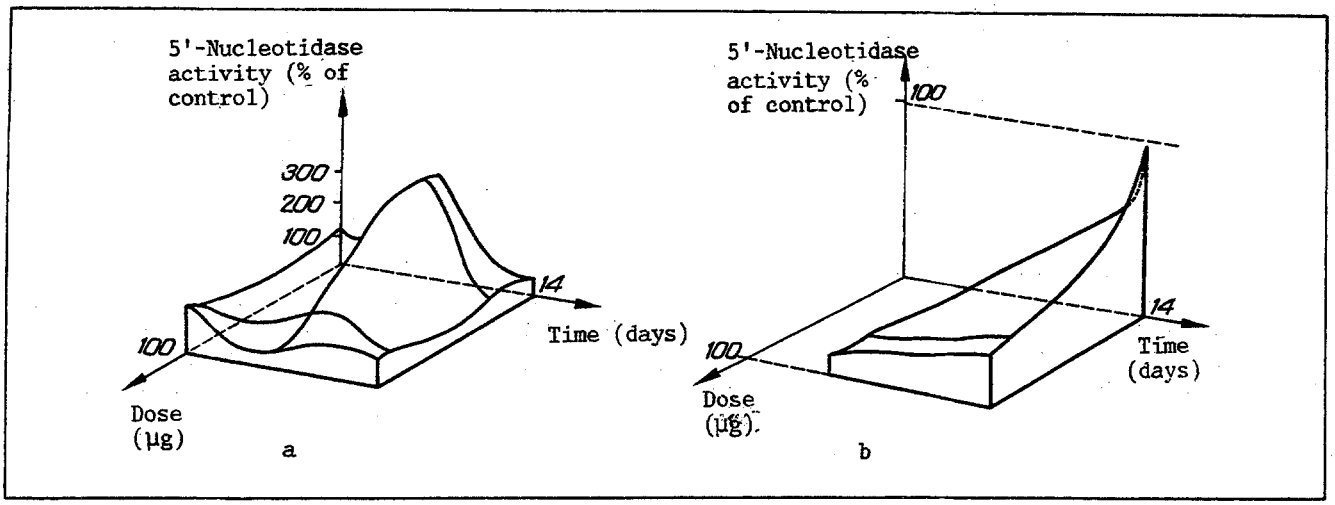

Fig. 2. Planimetric representation of two-factor regression models describing dependence of 5'-nucleotidase activity in MPS on dose of salmosan and on time elapsing after its injection: a) subcutaneous injection of salmosan, b) intraperitoneal injection.

time elapsing after its injection (Fig. 2) [1]. As Fig. 2 shows, after subcutaneous injection of salmosan into CBA mice, changes in 5'-N activity were phasic in character. An increase in activity compared with the control was predominant, and the depth of the metabolic changes increased with a decrease in the dose of the preparation. After intraperitoneal injection of salmosan, however, a significant decrease in 5'-N activity was observed, and its depth increased with an increase in dose of the preparation.

If the views on correlation between 5'-nucleotidase activity in MPS and sensitivity to the toxin expressed above are correct, a glance at Fig. 2 may suggest that subcutaneous injection of salmosan ought to be accompanied by increased sensitivity to the toxin, but intraperitoneal injection by a decrease. Under these circumstances, the maximum of the change in enzyme activity ought to correspond to the maximal change of sensitivity to the toxin. The investigation confirmed this suggestion. For instance, the greatest increase in sensitivity to the toxin was observed 7 days after subcutaneous injection of salmosan in a dose of 10 μg per mouse (LD_{50} in the experimental group was 1.58 times lower than in the control, where LD_{50} was 5.2 μg), A maximal increase in 5'-N activity was observed in the mice of this experimental group (Fig. 2). The greatest decrease in sensitivity to the toxin (LD_{50} of the experimental group was 1.9 times higher than in the control) was observed 1 day after intraperitoneal injection of salmosan in a dose of 100 μg. As will be clear from Fig. 2, it was in this group of animals that the greatest decrease in enzyme activity was noted.

To summarize the facts described above it must be emphasized once again that analysis of the data indicates that the level of activity of ecto-5-nucleotidase in peritoneal macrophages of CBA mice is a factor determining sensitivity to murine toxin.

This conclusion is in agreement with the results of an investigation by T. C. Montie et al. [7], according to which cAMP is an antagonist of the lethal activity of fraction II. 5'-N, as we know, is a physiologically important regulator of the cAMP level [6]. It can be postulated that correlation between sensitivity to murine toxin and the level of 5'-N activity can be explained on the grounds that the activity of this enzyme reflects a change in the endocrine status of the animal. In particular, the study of the effect of salmosan on parameters of the immune and neuroendocrine systems has shown that the level of 5'-N activity in MPS is closely linked with the glucocorticoid level [2]. The toxic syndrome following injection of fraction II of *Y. pestis* resembles the picture of functional adrenalectomy [7]. In order to shed light on the molecular mechanisms of correlation between the level of 5'-N activity in MPS and sensitivity to fraction II, further investigations are needed with highly purified murine toxin, the principal component of fraction II. Even at this stage, however, it can be confidently stated that the level of 5'-N activity in macrophages is an important pathogenetic factor in plague toxemia. In research into the pathogenesis of plague, more attention must therefore be given to the state of the mononuclear phagocyte system and to the study of the cytoplasmic membrane of macrophages.

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CHARACTERISTICS OF PERIPHERAL BLOOD LYMPHOID SUBPOPULATIONS OF SHIGELLOSIS PATIENTS

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The writers showed previously [1, 2] that in inflammatory diseases of the large intestine characterized by the common nature of the principal symptoms of the disease (exacerbation of a chronic recurrent form of nonspecific ulcerative colitis – NUC – and the acute form of bacterial dysentery – BD), destabilization of immune homeoctasis is observed, one manifestation of it being a disturbance of relations of immune regulatory lymphocytes both with one another and with other immunocompetent cells. Changes such as a decrease in the total number of T-l, $T\gamma^-$, and theophylline-sensitive lymphocytes and an increase in the number of T-active lymphocytes and immature postthymic cells (theophylline-dependent), in NUC and BD are common in character. The differences between them are: 1) in BD there is no increase in the number of O lymphocytes (O-l) and lymphocytes forming rosettes with autologous erythrocytes; 2) in 20% of patients with BD the number of $T\gamma^+$ lymphocytes in a mononuclear suspension exceeds the number of E-RFC (in patients with NUC the percentage of $T\gamma^+$-l is inversely proportional to the severity of the patient's condition); 3) during determination of the content of $T\gamma^-$-l and $T\gamma^+$-l and of theophylline-resistant and theophylline-sensitive lymphocytes (tpr-l and tps-l) in an enriched T-l cell suspension, an equivalent distribution of $T\gamma^+$-l and tps-l was observed in patients with BD, but there was no correspondence between them in NUC [1].

There is no doubt that disturbances of relations between immunoregulatory subpopulations of lymphocytes involve changes in the character of their action on mutually subordinate systems, and in turn, this determines the course of the pathological process, its outcome, and the efficacy of ways and means of immunocorrection. Particular features of the phenotype and function of lymphocytes during an exacerbation in patients with NUC were examined by the writers previously [3, 4].

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