IMMUNOMODULATING ACTION OF HISTAMINE IN INBRED MICE

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There is abundant experimental evidence that biogenic amines, and histamine in particular, play a direct role in the regulation of immunologic processes [1, 2]. However, the immunomodulating action of histamine has been studied as a rule in cell culture. However, representation of the manner in which this biogenic amine is involved in immunoregulatory processes under conditions as close as possible to the real situation, is complicated by the difficulty of extrapolating data obtained in cell culture to processes in the whole body.

The aim of this investigation was to study the immunomodulating action of histamine at the whole body level. A method of estimating immunomodulating activity (IMA) of a preparation based on a change in the level of 5-nucleotidase activity in peritoneal exudate macrophages (PEM) was used in the investigation. This method of primary screening of immunomodulators was developed at the N. F. Gamaleya Institute [6].

EXPERIMENTAL METHOD

Experiments were carried out on inbred male mice weighing 16-18 g: CBA, C57BL/6, BALB/C, NFR/n, and NFS/n. Histamine was injected subcutaneously into the mice in doses of 1 to 100 μg. Activity of 5'-nucleotidase (5'-N) was determined in PEM by the method in [6] 24 h after subcutaneous injection of histamine. Animals receiving isotonic sodium chloride solution served as the control. The experimental results were subjected to statistical analysis [4].

EXPERIMENTAL RESULTS

Dose–effect curves for mice of different strains 24 h after subcutaneous injection of histamine are shown in Fig. 1. 5'-N activity was expressed as a percentage of the level of activity of the enzyme in PEM of control animals. As Figure 1 shows, CBA mice are areactive with respect to this metabolic characteristic when histamine was used in a dose of between 1 and 50 μg. Only if histamine was used in a dose of 100 μg was 5'-N activity observed to decrease. In C57BL/6 and BALB/C mice, when histamine was used in doses of 1 and 8 μg, activity of the enzyme was lowered. If the dose used was 25 μg, this parameter returned to normal, and subsequently the 5'-N activity decreased with an increase in the dose of histamine up to 43 μg. With a further increase in the dose, 5'-N activity in C57TBL/6 mice returned to its initial level, whereas in BALB/C mice 5'-N activity continued to remain below the control level. Thus the behavior of 5'-N activity in C57BL/6 mice repeated in its general features the changes in enzyme activity in BALB/C mice. The latter, however, were characterized by more marked metabolic changes, as may be seen particularly clearly when histamine was used in doses of between 50 and 100 μg.

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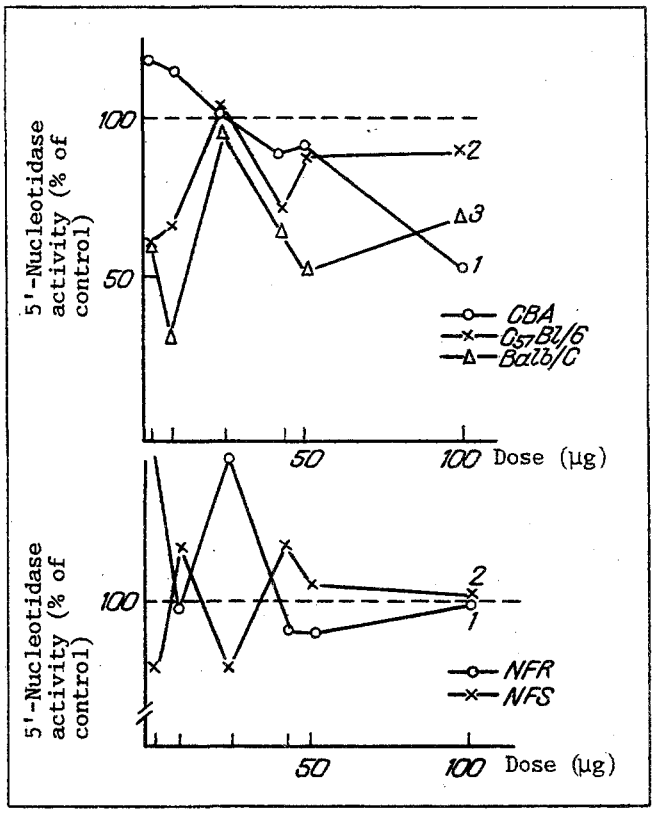

Fig. 1. Changes in 5-nucleotidase activity in PEM of mice of different strains in response to subcutaneous injection of histamine (in % of control).

NFR/n and NFS/n mice, when given histamine in doses of between 43 and 100 μg, were areactive with respect to this feature (Fig. 1). After injection of histamine in doses of between 1 and 43 μg, changes in 5′-N activity, just as in C57BL/6 and BALB/C mice, were phasic in character. When histamine was given in doses of 1 and 25 μg, changes in 5′-N activity in NFR/n and NFS/n mice were opposite in direction. In NFS/n mice, for example, a decrease was observed, whereas in NFR/n mice 5′-N activity was increased, and the increase was greater when histamine was given in a dose of 1 μg.

Analysis of the results indicates profound interlinear differences in the effect of histamine on the level of 5′-N activity in PEM. Maximal changes in 5′-N activity was observed in BALB/C and C57BL/6 mice, minimal in CBA mice. In mice of all strains studied (except CBA), maximal changes in enzyme activity were observed when small doses of histamine were used. For instance, interlinear differences in the character of the change in 5′-N activity in PEM were observed when histamine was used in a dose of 1 μg per mouse.

The opposite direction of the changes in 5′-N activity in histamine-sensitive (NFS/n) and histamine-resistant mice (NFR/n) will be noted. Difference in sensitivity to histamine is reflected in the character of the change in 5′-N activity. This state of affairs is in agreement with experimental results obtained in recent years showing close correlation between 5′-N activity and histamine receptors of PEM [5, 7].

5′-N (EC 3.1.3.5) is an enzyme of adenosine metabolism which plays an important role in the regulation of immunologic processes. The level of 5′-N activity in PEM is a factor in natural resistance and, in particular, resistance to infectious diseases [3].

Considering that one of the main problems in neuroimmunology is the lack of study of the mechanisms responsible for contrary effects of biogenic amines on the immune process, attention must be concentrated on the study of the effect of histamine on 5′-N activity under conditions when the opposite nature of the metabolic response is exhibited to the greatest degree. Since determination of the level of 5′-N activity in PFM is one way of assessing the immunomodulating activity of

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.

LITERATURE CITED

1. V. V. Abramov, Interaction of the Immune and Nervous Systems [in Russian], Moscow (1988).
2. A. A. Zozulya, Immunologiya, No. 5, 37 (1986).
3. G. B. Kirillicheva et al., Abstracts of Proceedings of the 7th Congress of the I. I. Mechnikov All-Union Society of Epidemiologists, Microbiologists, and Parasitologists [in Russian], Alma-Ata (1989), p. 57.
4. G. A. F. Seber, Linear Regression Analysis, Wiley, New York (1977).
5. P. V. Sergeev and N. Ya. Shimanovskii, Receptors [in Russian], Moscow (1987), pp. 278-279.
6. M. A. Tumanyan and G. B. Kirillicheva, Inventor's Certificate 1210790 USSR; Byull. Otkrytii, No. 6 (1985).
7. T. N. Shchukovskaya et al., Abstracts of Proceedings of the 5th All-Union Symposium on Interaction between Nervous and Immune Systems [in Russian], Orenburg (1990), p. 84.

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

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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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