CIRCADIAN RHYTHM OF ACTION OF IMMUNOMODULATOR MOP-35 ON MACROPHAGAL 5-NUCLEOTIDASE ACTIVITY

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The role of the neuroendocrine system in nonspecific regulation of immunologic functions, including functional activity of phagocytic cells, is now well known [1]. There is evidence that the action of immunomodulators on the metabolic potential of macrophages depends on the initial level of the endocrine parameters and, in particular, on the glucocorticoid hormone levels [4]. The glucocorticoid hormone levels have been shown to undergo considerable fluctuations during the 24-h period, with maximal concentration in mice in the evening and minimal in the morning. If the first assumption that the action of immunomodulators (IM) depends on the initial level of these hormones is true, we can postulate that effects of IM on the metabolic potential of the macrophages will be different in the evening and morning.

The aim of this investigation was to study the action of the immunomodulator MOP-35 on 5'-nucleotidase (5-NA) activity of peritoneal exudate macrophages (PEM), depending on the time of day, which is characterized by different glucocorticoid hormone levels.

EXPERIMENTAL METHOD

Experiments were carried out in winter. Male CBA and C57BL/6 mice were used. The IM MOP-35, a high-molecular-weight compound containing germanium, was injected intravenously and subcutaneously in doses of 10^{-4} and 10 μg per mouse. The doses were chosen on the basis of previous investigations. The compound was injected at 6 a.m., noon, and 6 p.m.; control animals were given an injection of isotonic NaCl solution. Each experimental group, containing not less than 6-8 animals, was accompanied by its control. The experimental and control mice were kept under identical standard conditions. After injection of IM, 5-NA activity was determined in the membrane of intact PEM. At the time of injection of the preparation blood levels of cortisol (by a fluoroimmunometric method [10]) and corticosterone (by radioimmunoassay [2]) were determined.

EXPERIMENTAL RESULTS

The results of determination of 5-NA activity in PEM 5 min after intravenous injection of MOP-35 at different times of the 24-h period in CBA and C57BL/6 mice are shown in Fig. 1. It will be clear from Fig. 1a that in CBA mice receiving an injection of IM at 6 a.m. a decrease in 5-NA activity was observed after only 5 min, and was about equal when doses of 10 and 10^{-4} μg were used. Quite the opposite effect was observed in the evening, when an

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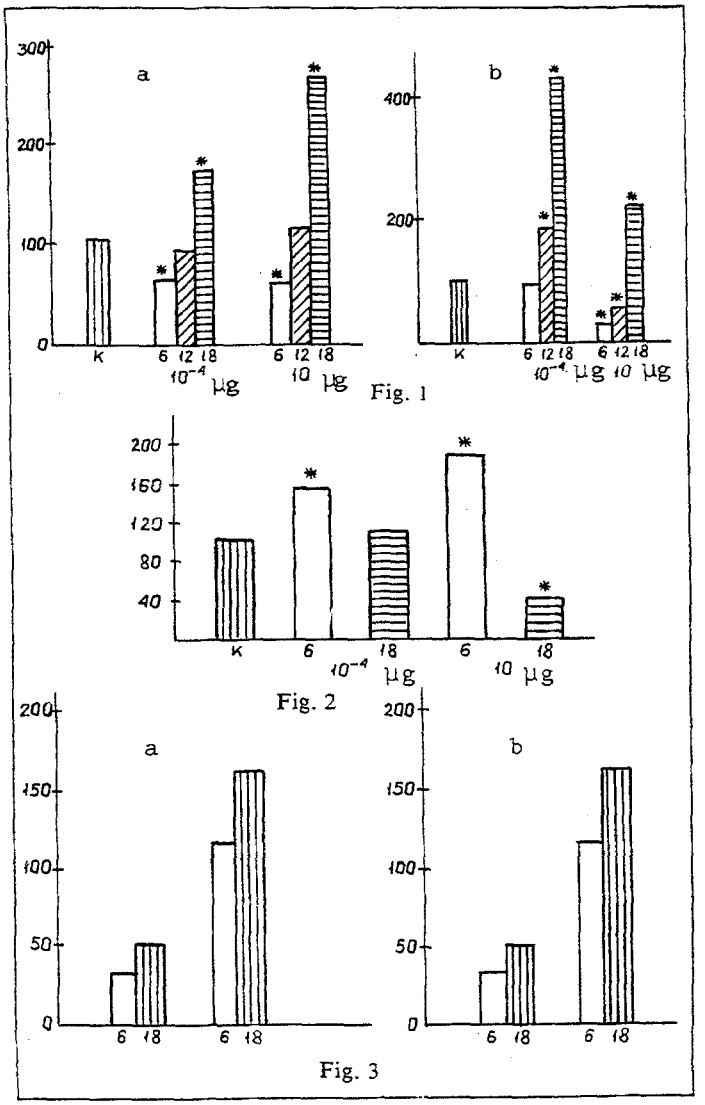

Fig. 1. 5′-Nucleotidase activity of PEM 5 min after intravenous injection of MOP-35 at different times of 24-h period in CBA (a) and C57BL/6 (b) mice. Abscissa, clock time; ordinate, 5-NA activity (in % of control, K). Asterisk indicates statistically significant differences from control ($p < 0.01$).

Fig. 2. 5′-Nucleotidase activity of PEM 24 h after subcutaneous injection of MOP-35 at different times of 24-h period in CBA mice. Legend as to Fig. 1.

Fig. 3. Blood levels of corticosterone (a) and cortisol (b) of CBA and C57BL/6 mice at different times of 24-h period. Horizontally – clock time; ordinate, concentration of corticosterone (in ng/ml) and cortisol (in nmoles/liter).

increase in 5-NA activity was observed after injection of IM in both doses, but slightly more marked when a dose of 10 μg was given. If the compound was injected at noon, no effect on enzyme activity could be observed. In C57BL/6 mice, just as in CBA, the effect depended on the time of administration (Fig. 1b). For instance, when the injection was given at 6 a.m., only when a dose of 10 μg was used was a decrease in 5-NA activity observed. If the compound

was injected at noon, a change in enzyme activity was observed not only when a dose of 10 μg was given, but also when a dose of 10^{-4} μg was given (an increase in 5-NA activity). If the compound was injected at 6 p.m., its action was opposite to the effect observed in the morning (IM in both doses caused a significant increase in 5-NA activity, which was more marked when the small dose was used).

Thus the character of the action of IM on 5-NA activity, when injected intravenously, in both strains of mice depended on the time of injection of the compound. Similar results were obtained when the MOP-35 was injected subcutaneously (Fig. 2).

Analysis of the results shows that by changing only the time of administration and keeping the other conditions unchanged (strain of mice, mode of injection, dose of IM) opposite effects can be obtained.

5'-Nucleotidase, an ectoenzyme of the cytoplasmic membrane of macrophages, is an important factor in the natural resistance of the body. There is evidence that 5-NA activity is connected with the level of natural resistance of the organism to infection, and with the radioresistance of animals [3, 5]. That is why the results of the present investigation showing that the character of action of IM on 5-NA activity of PEM depends on the time of day suggests that the action of IM on integral parameters such as sensitivity to infectious diseases and radioresistance, will also depend on the time of day.

This state of affairs is in agreement with the results of other investigations in which the immunomodulating effect of various preparations was shown to be dependent on the time of day [9].

The present study showed that the greatest differences in the character of the change in 5-NA activity of PEM, following administration of an immunomodulator, are observed after injection of the preparation at times which correspond to the greatest differences in blood levels of the glucocorticoid hormones (Fig. 3).

It was shown previously that in the immunomodulating effect correlation exists between 5-NA activity of PEM and the endogenous cortisol level [6]. The role of glucocorticoid hormones in regulation of the functional activity of the mononuclear phagocyte system is now well established [1]. Considering the close connection found between phagocytic cells and the neuroendocrine system, and in particular, 5-NA activity of the macrophages and the blood levels of glucocorticoid hormones, it can be tentatively suggested that one of the factors determining the pattern of action of immunomodulators on activity of this enzyme of PEM depending on the time of day is a particular feature of circadian rhythms of glucocorticoid hormones.

The investigation thus showed that by changing only the time of administration of IM it is possible to obtain a diametrically opposite effect on activity of 5-NA, an enzyme which plays an important role in the regulation of immunologic processes.

Dependence of the action of immunomodulators on biological circadian rhythms of the immune and neuroendocrine systems increases the likelihood of considerable variability of the immunomodulating effect, or even opposite effects on the same preparation, which means that the problem of immunomodulation is one of the most difficult in medicine and biology. The use of the circadian time factor opens up new prospects for the oriented regulation of the action of immunomodulators on immunologic processes.

REFERENCES

1. A. G. Belykh and P. V. Sergeev, Farmakol. Toksikol., No. 6, 102 (1984).
2. L. G. Zaitseva and Yu. N. Favorskaya, Byull. Éksp. Biol. Med., No. 11, 576 (1980).
3. L. A. Zakharova and R. V. Petrov, Progress in Science and Technology. Series: Immunology [in Russian], Vol. 25, Moscow (1990), pp. 6-47.
4. A. A. Zozulya and S. F. Pshenichkin, Progress in Science and Technology. Series: Immunology [in Russian], Vol. 25, Moscow (1990), pp. 48-120.
5. G. B. Kirillicheva, V. A. Bekhalo, M. S. Solov'eva, et al., Immunomodulators in Infectious Pathology [in Russian], Moscow (1988), pp. 105-108.
6. G. B. Kirillicheva, M. S. Solov'eva, E. V. Ermolova, et al., Abstracts of Proceedings of the 17th Congress of the I. I. Mechnikov All-Union Society of Epidemiologists, Microbiologists, and Parasitologists [in Russian], Alma-Ata (1989), p. 57.
7. G. B. Kirillicheva, V. V. Mitkin, M. S. Solov'eva, et al., Byull. Éksp. Biol. Med., No. 9, 280 (1991).

8. Yu. B. Lishmanov, L. N. Maslov, L. V. Maslova, et al., Patol. Fiziol. No. 4, 79 (1990).
9. M. A. Tumanyan and G. B. Kirillicheva, Otkrytiya, No. 6, 621 (1986).
10. M. R. Shurin, S. F. Pshenichkin, and A. A. Zozulya, Immunologiya, No. 6, 76 (1990).
11. E. Contreras, A. Germany, and M. Villar, Gen. Pharmacol., **21**, No. 5, 763 (1990).
12. I. V. Eskola et al., Clin. Chem., **31**, No. 1, 1731 (1985).
13. E. G. Fischer, Psychother. Psychosom. (Basel), **42**, No. 28, 195 (1984).
14. D. Malec and E. Michalska, Pol. J. Pharmacol. Pharm., **42**, 1 (1990).
15. S. Larulata, R. J. Simpson, and T. I. Webster, Clin. Exp. Immunol., **66**, 158 (1986).

DISTRIBUTION OF INDIVIDUAL CIRCULATORY BIORHYTHMS IN SCHOOLCHILDREN AGED 7-17 YEARS LIVING AT DIFFERENT ALTITUDES IN THE MOUNTAINS

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The temporal organization of hemodynamic processes in permanent dwellers at high altitudes is of definite interest because biorhythmologic methods can broaden qualitatively our knowledge of a given functional system, changes in which play a key role in adaptation to a mountain climate. This explains the recent increase in the volume of research undertaken to study this problem [1-7]. However, the publications cited above represent the results of group comparisons of biorhythms of the circulation in inhabitants of different mountain zones. Yet, however, when problems of population adaptation are being considered, attention must be paid to interindividual differences in biorhythms [8, 9]. Besides an analysis of averaged data, the aim of the present investigation was also to assess the character of distribution of individual biorhythms depending on the height at which the population lives.

EXPERIMENTAL METHOD

To ensure maximal standardization of the subjects with respect to age, sex, and social organization, the investigation was based at boarding schools situated at altitudes of 760, 1700, and 2850 m above sea level. In each altitude zone 90 schoolchildren were investigated, divided into three groups depending on their age: 7-10, 11-14, and 15-17 years (30 in each group). The parameters of the systemic circulation were assessed by the electrical impedance method of Kubicek et al. [10] six times in the course of the 24-h period, i.e., every 4 h.

The primary data were analyzed by the special "Cosinor" chronobiological program.

The character of distribution of individual biorhythms in the populations was estimated as the circadian course of the cardiac index (CI), the ratio of the cardiac output to the body surface area. This was because this index eliminates natural anthropometric differences between the subjects studied.

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