crease in the number of suppressor T cells in the body leads to inhibition of proliferation. A new biological function of the regulatory subpopulation of lymphocytes has been discovered: "surveillance" of cellular proliferation. The mechanism of realization of this function is not yet known, and experimental investigation is therefore necessary. It can be tentatively suggested that this function of the suppressor T cells plays an important role in the maintenance of homeostasis, and its study will open up new prospects for the correction of various pathological states.

LITERATURE CITED

1. A. G. Babaeva N. A. Kraskina, and L. D. Liozner, Tsitologiya, No. 12, 1511 (1969).
2. A. G. Babaeva, N. A. Kraskina, and N. V. Yudina, Byull. Éksp. Biol. Med., No. 1, 69 (1980).
3. N. A. Kraskina, T. K. Lopatina, and A. I. Mokrenko, Immunologiya, No. 4, 50 (1980).
4. N. A. Kraskina, M. S. Blyakher, T. K. Lopatina, et al., Cellular and Molecular Mechanisms of Anti-infectious Immunity [in Russian], Moscow (1983), pp. 27-27.
5. V. I. Kuvakina, M. A. Smirnova-Mutusheva, and N. V. Kholchev, Zh. Mikrobiol., No. 4, 63 (1974).
6. A. I. Mokrenko, Byull. Éksp. Biol. Med., No. 9, 339 (1980).
7. G. W. Snedecor, Statistical Methods in Application to Research in Agriculture and Biology, Iowa State Univ. Press, Ames, Iowa (1956).

MODEL TO LOOK FOR AFFERENT SIGNALS FROM THE IMMUNE TO THE NERVOUS SYSTEM

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Numerous investigations have demonstrated close interaction of the immune and nervous systems in the response of an organism to an antigen [3, 13]. Factors acting on particular structures of the CNS have been shown to modify the microenvironment of lymphoid cells, the number of circulating antibodies, the intensity of cellular reactions of immunity, and the ratio between numbers of lymphocytes in subpopulations [4, 10]. In turn, deep brain structures react to injection of antigens by persistent and reproducible restructuring of neuronal activity, the level of excitability, and the time course of bioelectrochemical potentials [1, 2]. Methods and channels of transmission of information from the immune system (IS) to the brain constitute the least studied aspect of interaction between the nervous and immune systems.

There is evidently not only one method of transmission of information from the IS to the CNS, but the chemical nature of the carriers of the afferent signals also may be different. The greatest interest from this point of view is aroused by regulators, synthesized in the IS and CNS, such as histamine, serotonin, prostaglandins, endorphins, enkephalins, and ACTH. In the opinion of some workers the role of carrier of afferent information may be performed by interferon, which has a common amino-acid sequence with ACTH and β-endorphin [11, 12], by interleukin-1 [10], and by a myelopeptide, isolated from bone marrow, which possesses not only immunologic activity, but also various neurotropic properties [5]. A possible role of substance P and of somatostatin in this process also has been suggested [14, 15].

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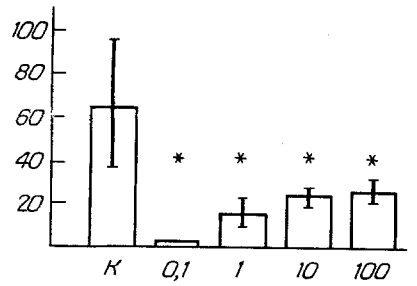

Fig. 1. Changes in number of antibody-forming cells in mouse spleen in response to injection of sheep's red blood cells and under the influence of the polarin SKD. Abscissa, doses of compound (in μg/kg); ordinate, number of antibody-forming cells per 10^6 nucleated cells (in %). K) Control. Asterisk indicates significant difference from control.

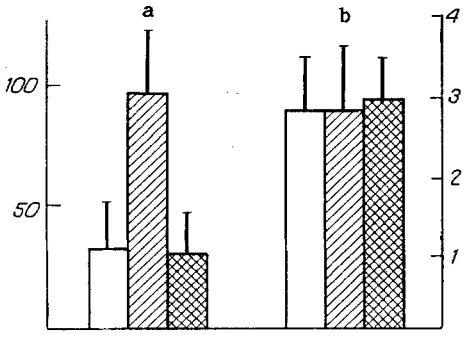

Fig. 2. Effect of polarin SKD on survival rate (a) and area of involvement of lungs (b) in mice infected with 0.1 LD_{50} of influenza virus. Ordinate: on left) survival rate (in %), on right) area of invovlement of lungs (in points, on Lindeman's scale). Unshaded columns) control, obliquely shaded) injection of polarin SKD in a dose of 1 mg/kg, cross-hatched) in a dose of 100 μg/kg.

All these candidates for the role of information transmitters from the IS to the nervous system are polypeptides, in whose composition there are identical amino acids, alternating in such an order that some of the oligopeptides composing them are similar. This fact suggests a possible role not of the whole molecules of these polypeptides in the transfer of information from the IS to the CNS, but also of their parts, and it is accordingly logical to attempt to look for artificial or natural oligopeptides with the minimal number of amino acids, administration of which will completely or partially reproduce the response of brain structures to an antigen and will influence the functions of the IS.

In order to look for material carriers of information whereby the IS interacts with the CNS, we developed the following working hypotheses.

1. The language by which information is exchanged between the systems must be universal and must be received and translated (recorded) equally well by the two systems: immune and nervous.

2. The most probable material carriers of information are peptide–protein bioregulators, functioning both in the IS and in the CNS.

3. Since the majority of immunoregulators (mono- and lymphokines, interferons, interleukins, thymus hormones, etc.) have high molecular weights, and since the classical neuro-

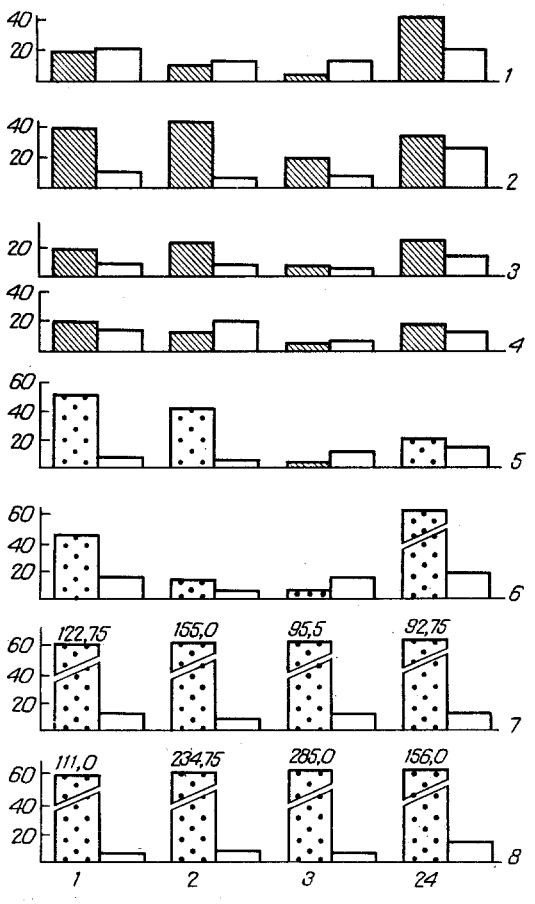

Fig. 3. Changes in electrical potential in deep brain structures of rabbits produced by polarin SKD. Abscissa, time after injection of preparation (in h); ordinate, change in potential relative to initial value, taken as 0 (in %). 1) Lateral nuclei of amygdala; 2) basal nuclei of amygdala; 3) medial preoptic region; 4) posterior hypothalamic field; 5) central nucleus raphe; 6) locus coeruleus; 7) gigantocellular nucleus raphe; 8) hippocampus. Unshaded columns) control animals, shaded) experimental animals.

transmitters are small in size, the possibility cannot be ruled out that the active units, the carriers of information,may be oligopeptides – products of restricted proteolysis of peptides and proteins, for example, the so-called thetins [6, 7, 9].

4. The most probable ways of formation of oligopeptides from precursor proteins during interaction between T and B lymphocytes and macrophages are: a) restricted proteolysis of proteins actually on the surface membranes of the interacting cells, by proteases located there (similarly to processes of membrane digestion), b) proteolysis taking place as a result of the action of proteolytic enzymes secreted by the cells during their cooperation in the microenvironment, i.e., in the immunosynapse, and c) restricted proteolysis of precursor proteins in cell vacuoles arising during endocytosis of immune or ligand–receptor complexes, the components of which are immunoglobulins, monokines and lymphokines, proteins of the major histocompatibility complex, etc. Special attention is deserved by the third possible pathway of biogenesis of oligopeptides, includig the thetins, in view of the universality and the wide distribution of processes of endocytosis and exocytosis in various immunologic reactions. In this case the thetins formed act inside the cell and/or are secreted into the intercellular space during exocytosis.

To test the above hypotheses it was decided to look for common structural fragments in peptides and proteins functioning in the IS and CNS, as potential sources for the formation of active mediator substrates, the synthesis of the corresponding peptides, investigation of their neurotropic and immunotropic activity and, most important of all, discovery of their formation and functioning in vivo.

Among the list of the possible, or even the most probable, candidates for the role of information carriers among the low-molecule-weight peptides that may be formed and may function in the IS and CNS, and may play the role of carriers of afferent signals, are peptides of the polarin type, constructed mainly from polar amino acids, for segments of polar amino acids, often encountered in immunoactive and neuroactive peptides and proteins, may serve as their precursors [8, 9].

To test this hypothesis, we chose as the first model compound a tripeptide of the polarin group, Ser-Lys-Asp (SKD), containing functionally active OH, α- and ε-, and α- and β-COOH groups. Fragments of this type are located in functionally active centers of many immunoregulators and neuropeptides [8].

The fragment was synthesized by a solid-phase method, using a copolymer of styrene and divinylbenzene, with 1% cross-linking, as the carrier. The peptide is characterized by the following constants: mobility 0.16 (thin-layer chromatography on silica-gel in a $CHCl_3$–Ch_3COOH–H_2O system in the ratio 5:6:2), E_{His} = 0.91 (electrophoresis on paper in 1 M CH_3COOH), [α_D^{20} = 12.3°, CH_3COOH].

The experiments revealed a broad spectrum of biological activity of the SKD tripeptide. It was found to act highly differentially on the IS, depressing antibody-forming cells in response to injection of high doses of antigen (sheep red blood cells; Fig. 1). Its addition to the incubation medium of peripheral blood leukocytes from cancer patients reduced the increased and normal functional activity of natural killer cells. The tripeptide had a protective action against viral infection in mice (Fig. 2).

A single intravenous injection of the peptide in a dose of 300 μg caused significant changes in bioelectrical activity of structures of the rabbit CNS, which were revealed by electrophysiological investigations of the time course of the bioelectrochemical potentials of eight deep brain structures, by the use of gold electrodes. It was shown that during the first hour similar changes of potential develop in the lateral and medial nuclei raphe and the corticomedial nuclei of the amygdala. Changes of opposite sign were observed in the region of the locus coeruleus and hippocampus. No signficant changes were found in structures of the anterior and posterior hypothalamus. Incidentally, having reached their maximal value during the first hour, the changes of potential then continued at this level throughout the period of observation until 24 h.

The investigations, based on theoretical assumptions of the possible biological activity of oligopeptides containing polar amino acids revealed some neurotropic and immunotropic effects of polarin SKD. It can be tentatively suggested that this oligopeptide, a fragment present in the functionally active centers of many immunopeptides and neuropeptides, and possessing high biological activity, may be a suitable chemical model of the afferent information carrier from the immune system to the nervous system (Fig. 3).

The study of the biological activity of the polarins deserves attention as a fully independent section of research into a new class of peptides, and it is evidently of practical importance. The first results, obtained in the present investigation, are compatible with the theoretical assumptions which have been suggested, and they may serve as indirect evidence in their support; they indicate the desirability of a further study of oligopeptides as possible transmitters of information from the immune system to the nervous system and, consequently, as immunoregulators.

LITERATURE CITED

1. V. A. Grigor'ev and V. M. Klimenko, Fiziol. Zh. SSSR, 70, No. 2, 221 (1984).
2. V. M. Klimenko, "The study of some neuronal mechanisms of hypothalamic regulation of immunologic responses in rabbits," Author's Abstract of Dissertation for the Degree of Candidate of Medical Sciences, Leningrad (1972).
3. E. A. Korneva, V. M. Klimenko, and É. K. Shkhinek, The Neurohumoral Maintenance of Immune Homeostasis [in Russian], Leningrad (1978).

4. E. A. Korneva, Vestn. Akad. Med. Nauk SSSR, No. 3, 63 (1985).
5. R. V. Petrov, R. A. Durinyan, A. M. Vasilenko, et al., Dokl. Akad. Nauk SSSR, 265, No. 2, 501 (1982).
6. G. I. Chipens, Vopr. Med. Khim., No. 3, 37 (1984).
7. G. I. Chipens, Izv. Akad. Nauk Latv. SSR, No. 12, 93 (1984).
8. G. I. Chipens, R. É. Vegner, N. G. Ievinya, and G. F. Rozental', Izv. Akad. Nauk Latv. SSR, No. 9, 85 (1985).
9. G. I. Chipens, R. É. Vegner, N. G. Ievinya, and G. F. Rozental', Izv. Akad. Nauk Latv. SSR, No. 9, 93 (1986).
10. H. O. Besedovsky, A. del Rey, and E. Sorkin, Immunoregulation, New York (1983).
11. J. B. Blalock, J. Immunol., 132, No. 3, 1067 (1984).
12. J. B. Blalock and E. M. Smith, Fed. Proc. Fed. Am. Soc. Exp. Biol., 44, No. 1, 108 (1985).
13. J. J. Cohen, Immunol. Today, 8, No. 2, 33 (1987).
14. D. G. Payan, J. D. Levine, and E. Y. Goetzl, J. Immunol., 132, 1601 (1984).
15. D. G. Payan, J. P. McGillis, F. K. Renold, et al., Second International Workshop on Neuroimmunomodulation, Dubrovnik (1986), p. 35.