2. V. V. Abramov, V. G. Bezgachev, N. Yu. Gromykhina, A. Ts. Batoeva, et al., Dokl. Akad, Nauk SSSR, **303**, No. 1, 249 (1988).
3. V. V. Abramov, T. Ya. Abramova, V. A. Mordvinov, and V. A. Kozlov, Dokl. Akad. Nauk SSSR, **311**, No, 1, 243 (1990).
4. V. V. Abramov, Usp. Fiziol. Nauk, **21**, No. 2, 111 (1990).
5. E. M. Volkov, G. A. Nasledov, and I. I. Poletaev, Byull. Éksp. Biol. Med., No. 3, 24 (1982).
6. G. F. Lakin, Biometrics [in Russian], Moscow (1980).
7. A. G. Mustafin, V. N. Yarygin, and S. A. Prokov'ev, Byull. Éksp. Biol. Med., No. 9, 343 (1989).
8. N. V. Nechaeva, T. V. Aizenshtein, and E. A, Luria, Tsitologiya, **12**, No. 4, 465 (1970).
9. M. R. Sapin, The Lymph Node [in Russian], Moscow (1978).
10. A. J. Cunningham, Nature, **207**, 1106 (1965).

THE NEUROENDOCRINE SYSTEM AND SPECIFIC FACTORS OF IMMUNITY IN PESTICIDE POISONING

A. A. Khusinov, D. S. Khaidarova, G. V. Gushchin, and M. P. Lesnikova

UDC 615.285.7.099].015.4:
612.017.1].07:612.43/.45

KEY WORDS: pesticides; neuroendocrine regulation; immunity.

The problem of neuroendocrine regulation of immunologic functions has been the subject of study by Soviet [3, 4, 7, 8] and Western [16, 18] workers. However, we could find no information in the accessible literature on the neuroendocrine regulation of immunogenesis studied in chronic pesticide poisoning. Nevertheless, there is evidence in the literature that pesticides have a harmful action on factors of immunity, including the toxic action of small doses of pesticides [2, 6, 17].

Investigations into the effect of organophosphorus compounds (OPC) on the state of the hypothalamo-hypophyseal neurosecretory and hypothalamo-hypophyseal-adrenocortical systems (HHNS and HHACS) conducted previously in the writers' department revealed phasic changes in the above-mentioned systems with activation of their functional state after 1 and 3 months of poisoning. In chronic experiments an increase in the content and a change in the relative content of 11-hydroxycorticosteroids, hydrocortisone, and corticosterone were found in the peripheral blood after poisoning with small doses of OPC [5, 11-13].

The aim of this investigation was to compare the effect of chronic poisoning with the OPC Antio (Formathion) on the state of the specific factors of immunity and on the blood level of corticosterone (CS), a glucocorticoid hormone.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 160-220 g, receiving Antio in a dose of 0.01 LD_{50} (3.5 mg/kg) daily perorally for 2 months. Animals of the control group received an equal volume of the solvent.

Department of Pathological Physiology, Samarkand Medical Institute. Department of General Pathology and Pathological Physiology, Research Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR A. D. Ado.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 112, No. 12, pp. 623-624, December, 1991. Original article submitted June 21, 1991.

 0007-4888/91/0012-1774$12.50 ©1992 Plenum Publishing Corporation

TABLE 1. Plasma Corticosterone Concentration (mg/ml) in Wistar Rats with Chronic Poisoning by OPC Antio

Time of observation, days	Corticosterone level	
	control	antio, 0.01 LD_{50}
	Basal level — 222,7±9,0 (9)	
30	240,0±30,0 (5)	408,3±86,9 (6)
60	286,2±62,0 (5)	673,3±56,7 (6)*

Legend. *) Statistically significant difference ($p < 0.001$) from control; numbers in parentheses give number of animals.

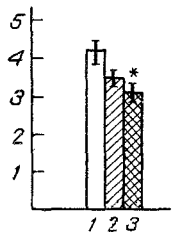

Fig. 3

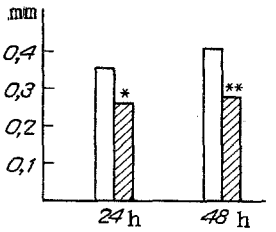

Fig. 4

Fig. 1. Hemagglutinin-titers of Wistar rats immunized with SRBC and poisoned with Antio. Animals injected intraperitoneally with SRBC in a dose of (1-5) · 10^9 cells in 1 ml physiological saline on 23rd and 53rd days of Antio poisoning HA titers determined 7 days after immunization. Abscissa, groups of animals: 1) control ($n = 10$), 2) Antio 0.01 LD_{50}, 30 days ($n = 8$), 3) Antio 0.01 LD_{50}, 60 days ($n = 8$). Ordinate, $\log_2$ of HA titers; *$p < 0.02$.

Fig. 2. Intensity of DTHR in Wistar rats subjected to chronic poisoning with OPC Antio. DTHR reproduced on 21st day after sensitization by injection of SRBC (10^8 cells) into animal's footpad. Reaction read as difference in diameter of limb after 24 and 48 h. Abscissa, time after induction of DTHR, in h; ordinate, intensity of DTHR, in mm. Unshaded columns — control animals ($n = 5$); obliquely shaded — poisoning with Antio in a dose of 0.01 LD_{50} for 60 days ($n = 5$); *$p < 0.02$, **$p < 0.01$.

The functional state of the immune system was assessed by the intensity of the humoral immune response, for which the titers of hemagglutinins (HA) were determined in the blood serum of rats immunized with sheep's red blood cells (SRBC) in a dose of (1-5) · 10^9 cells/ml, intraperitoneally, preceded by poisoning with Antio. The intensity of cellular immunity was determined in the animals by the delayed-type hypersensitivity reaction (DTHR), by injecting 10^8 cells in a volume of 0.1 ml physiological saline into the footpads and measuring the difference in the diameter of the limb before and 24 and 48 h after injection of the antigen.

The plasma CS concentration was determined by direct radioimmunoassay [1], using standard RIN-V-^{3}H kits. Blood for testing was obtained by immediate decapitation of the animals.

The results were subjected to statistical analysis by Student's t-test.

EXPERIMENTAL RESULTS

The results are given in Table 1 and Figs. 1 and 2.

As Table 1 shows, elevation of the CS level in the poisoned animals compared with data for the control group was observed on the 30th and 60th days of observation ($p < 0.001$). Determination of the HA titers (Fig. 1) revealed a decrease on the 30th and 60th days ($p < 0.02$) in animals of the experimental group relative to the control. As regards DTHR (Fig. 2) a decrease in its intensity was found compared with the control in the group of animals poisoned with Antio for 60 days ($p < 0.02$ and $p < 0.01$).

In previous studies of the effect of OPC on the morphological and functional state of the HHNS and HHACS and on the level of glucocorticoid hormones [5, 11-13] periods of activation of these systems followed by the development of a state of dysfunction were observed; the latter period. moreover, was characterized not only by changes in the absolute glucocorticoid levels, but also in their relative levels as a result of an increase in the CS concentration.

According to data in the literature, large pharmacologic doses of glucocorticoids, especially if administered for a long time, inhibit the humoral and cellular immune response [10, 14, 15]. On the basis of these findings, glucocorticoid hormones can be classed as inhibitors of metabolism of cells of the lymphoid series. The inhibitory action of glucocorticoids is due mainly to binding by specific cytoplasmic receptors and their subsequent translocation into the nucleus, where the hormonal signal is transformed into the biological response of the cell due to changes in the function of its nuclear apparatus [9].

In our investigations during OPC poisoning, elevation of the blood CS level as a rule coincided with a fall in the parameters of humoral and cellular immunity, evidence of inhibition of the immune response, which is evidently associated with increased CS secretion.

It can thus be concluded from the results of the present investigation, together with those of our previous studies, that enhancement of the functional activity of the HHNS and HHACS and elevation of the glucocorticoid hormone levels during long-term poisoning by the pesticide Antio, correlating in time with inhibition of the immune response, may be one of the mechanisms of lowered resistance of the body and increased prevalence of illness in regions where pesticides are used intensively.

LITERATURE CITED

1. N. P. Goncharov, V. I. Vorontsov, G. V. Katsiya, et al., Vestn. Akad. Med. Nauk SSSR, No. 8, 13 (1977).
2. P. G. Zhmin'ko, "Particular features of the biological action of the organophosphorus pesticide/acaricide cyclophos and its hygienic norms in the air of the working zone (experimental toxicologic-hygienic investigation)," Author's Abstract of Dissertation for the Degree of Candidate of Biological Sciences, Kiev (1988).
3. E. A. Korneva, Interaction between Nervous and Immune Systems under Normal and Pathological Conditions [in Russian], Leningrad (1987).
4. E. A. Korneva and E. K. Shkhinek, Hormones and the Immune System [in Russian], Leningrad (1988).
5. Ya. K. Kurambaev, "Effect of the organophosphorus chemical poison Antio on the adrenals and hypothalamo-hypophyseo-neurosecretory system," Author's Abstract of Dissertation for the Degree of Candidate of Medical Sciences, Leningrad (1986).
6. A. I. Nikolaev, L. A. Katsenovich, and Sh. T. Atabaev, Pesticides and Immunity [in Russian], Tashkent (1988).
7. G. N. Pershin, I. D. Frankel', and V. D. Sidorov, Immunologiya, No. 4, 7 (1985).
8. R. V. Petrov, Vestn. Akad. Med. Nauk SSSR, No. 8, 3 (1980).
9. V. B. Rosen and L. N. Smirnov, Receptors and Steroid Hormones [in Russian], Moscow (1981).
10. B. S. Uteshev and V.A. Babichev, Inhibitors of Antibody Biosynthesis [in Russian], Moscow (1974).
11. A. A. Khusinov and R. D. Dzhabbarov, The Endocrine System and Harmful External Environmental Factors [in Russian], Leningrad (1987), p. 240.
12. A. A. Khusinov, Ya. K. Kurambaev, Kh. T. Tavmuradov, et al., The Endocrine System and Harmful External Environmental Factors [in Russian], Leningrad (1987), p. 241.

13. A. A. Khusinov, Ya. K. Kurambaev and D. Kh. Ziyaeva, Disturbance of Mechanisms of Regulation and Their Correction [in Russian], Vol. 1, Moscow (1989), p. 217.
14. J. Ahlqvist, Psychoneuroimmunology, New York (1981), pp. 355-403.
15. E. Dupont, J. Wybran, and C. Toussaint, Transplantation, **37**, No. 4, 331 (1984).
16. W. J. Irvine, Immunology-80, London (1980), pp. 204-206.
17. C. Lafarge-Frayssint and E. Decloitre, J. Immunopharmacology, **4**, No. 2, 43 (1982).
18. E. Okaushi, J. Physiol. Soc. Jpn., **38**, 325 (1976).

ANTIBODY LEVELS TO DIFFERENT DETERMINANTS OF GROUP A STREPTOCOCCAL POLYSACCHARIDE AND AUTOANTIBODIES TO THE BASAL LAYER OF THE SKIN EPITHELIUM IN RHEUMATIC FEVER

N. A. Borodiyuk, E. A. Bazanova, I. M. Lyampert, A. V. Nekrasov, N. G. Puchkova, T. K. Asoskova, and E. S. Evtushenko

UDC 616-002.77-07: 616.157:579.862.1]-078.33

KEY WORDS: polysaccharide rheumatic fever; antibodies.

In various autoimmune processes in man and in New Zealand mice autoantibodies reacting with the basal layer of the skin epithelium (BLSE) and also with the epithelium of the cortical and medullary zones of the thymus [6], which is a type of endocrine epithelium [13], have been found It was shown previously that the streptococcal group A polysaccharide (A-PSC) contains a cross-reacting (CR) determinant, to which autoantibodies directed toward the above-mentioned epithelial cells of the skin and thymus mentioned above are directed [14]. During isolation of the antibodies by affinity chromatography it was shown that these reactions are linked with high-affinity antibodies to a group-specific (GS) determinant of A-PSC [5]. Similar reactions with epithelium of the thymus and skin have been found with the aid of monoclonal antibodies (MCA), obtained to one of the rhamnose determinants of A-PSC MCA evidently arising against another rhamnose determinant of A-PSC, react with all layers of epithelium of the skin and thymus [7]. It has been suggested that injury to the endocrine epithelium of the thymus by autoantibodies leads to immunoregulatory disturbances, namely to a deficiency of suppressor T cells, a characteristic feature of autoimmune processes [6].

A high level of antibodies to the GS determinant of A-PSC, containing β-N-acetylglucosamine, is found as a rule in primary active rheumatic fever (PAR), in a smaller percentage of cases in recurrent active rheumatic fever (RAR), in individual cases In an inactive phase of rheumatic fever, and in not more than 10% of control sera. Conversely, in PAR a high level of antibodies to rhamnose determinants of A-PSC is found in individual cases, and rather more often in healthy blood donors and patients with RAR [2, 3, 4]. Autoantibodies to BLSE and to epithelium of the cortical and medullary zones of the thymus have been found in a high percentage of cases in PAR, less frequently in RAR, and in individual cases in healthy controls [10]. These autoantibodies did not inhibit A-PSC in all cases, and it is not clear to which CR determinant of A-PSC they are directed. It likewise has not been established whether any connection exists between the presence of autoantibodies to BLSE and the level of antibodies to GS, and also to the rhamnose determinants of A-PSC in rheumatic fever and in healthy control sera Since a high level of antibodies to the GS determinant of A-PSC [2] and autoantibodies to BLSE [10] are observed very rarely in control sera, it is rational to undertake a special analysis of sera of the control group with a high level of antibodies to A-PSC.

N. F. Gamaleya Research Institute of Epidemiology and Microbiology, Academy of Medical Sciences of the USSR. Institute of Immunology, Ministry of Health of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Prozorovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 112, No 12, pp. 624-627, December, 1991. Original article submitted June 17 1990.