AUTOIMMUNE RESPONSE IN EXPERIMENTAL HIPPOCAMPAL PATHOLOGY

A. V. Martynenko, S. V. Magaeva,
L. A. Basharova, and M. V. Martynenko

UDC 616.831.314-092.9-092:612.017.1

KEY WORDS: hippocampal pathology; autoantibodies to neurotransmitters.

Experimental pathology of the limbico-diencephalic system of the brain modifies immunoreactivity [6, 8, 11] and may give rise to the development of secondary immunodeficiency states [3, 8]. On the basis of the concept of diseases of regulation [7] and modern views on mechanisms of neurohumoral control of immune responses [1, 6, 8, 11, 13], it can be postulated that certain forms of secondary immunodeficiency states are the result of pathology of the central apparatus of neurohumoral regulation of functions of the immune system. Since any form of CNS pathology is accompanied by disturbance of mediator metabolism, these disturbances are evidently an important stage in the pathogenesis of neurogenic immunodeficiency. The neurotransmitters noradrenalin (NA) and serotonin (5-HT) have been shown to be important factors in regulation of immunologic responses of functions of the immune system [1, 12]. This makes the possible induction of synthesis of antibodies against NA and 5-HT a particularly interesting topic.

Previous investigations have shown that in pathology of the main part of the limbic system of the brain, autoimmune responses to brain tissue antigens (TA) are induced [2].

The aim of this investigation was to study the possibility of synthesis of autoantibodies to NA and 5-HT and autoimmune responses to antigens of the hippocampus and viscera.

EXPERIMENTAL METHOD

Experiments were carried out on male Chinchilla rabbits weighing 2.5-3 kg. Animals in which no autoantibodies to NA and 5-HT or to TA of the hippocampus, heart, and lungs could be found were selected for the experiments. The right dorsal hippocampus was destroyed by electrocoagulation (dc anode, 3 mA, 12 V, 1 min) through a nichrome electrode, implanted chronically at coordinates AP 3.6 and D 1.5 taken from a stereotaxic atlas of the brain [15].

The electrode was inserted under local procaine anesthesia to a depth of 5.8-6 mm, with individual correction for the thickness of the bone. Anodal coagulation of the hippocampal structures was carried out 5 weeks after implantation of the electrodes. The location of the destructive foci was identified in frontal brain sections after the end of the experiment.

Blood was taken from the marginal vein of the ear 2, 3, 6, 10, and 20 weeks after trauma and serum levels of antibodies to NA and 5-HT determined. Antibodies were detected by the passive hemagglutination test with a red cell diagnostic serum prepared by the method in [10]. Antibodies to antigens from tissues of the hippocampus, heart, and lung were determined at the same times by the complement fixation test (CFT) in the usual way. Saline extracts (20%) were used as antigens. The specificity of complement-fixing antibodies to brain and heart tissue antigens was verified by a parallel CFT with TA of liver and skeletal muscle, respectively. The results were subjected to statistical analysis by Student's method. The antibody titer was expressed in $\log_2$ units. A 1:2 dilution of serum was taken as 1. Twenty rabbits with local hippocampal destruction and 16 control rabbits with an intact brain were used in the experiments.

Laboratory of Pathophysiology of the Immunity System, Research Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow (Presented by Academician of the Academy of Medical Sciences of the USSR G. N. Kryzhanovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 102, No. 7, pp. 10-11, July, 1986. Original article submitted March 22, 1986.

 0007-4888/86/0007-0878$12.50

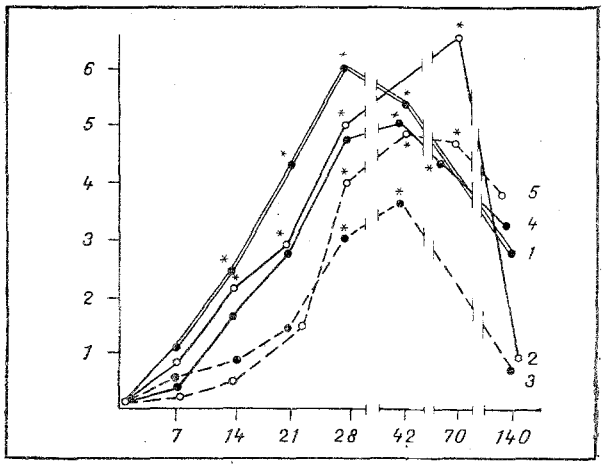

Fig. 1. Autoantibodies to neurotransmitters and tissue antigens (TA) of viscera following local hippocampal destruction. Abscissa, time after hippocampal destruction (in days); ordinate, logarithmic index of mean antibody titer ($\log_2$). Antibodies to: 1) Hippocampal TA, 2) NA, 3) 5-HT, 4) heart TA, 5) lung TA. Asterisk indicates significant difference.

EXPERIMENTAL RESULTS

Destruction of the hippocampus induced a series of autoimmune responses (Fig. 1). Antibodies to hippocampal TA were found in 43% of experimental animals 7 days after hippocampal destruction. After 14 days these antibodies were found in 80%, and after 28 to 56 days, in 100% of cases. The highest antibody titer was observed 28 days after hippocampal destruction.

Autoimmune responses to neurotransmitters were discovered for the first time in pathology of the nervous system. Antibodies to NA were discovered in 50% of experimental animals 2 weeks after hippocampal destruction. After 6 weeks these antibodies were found in all the rabbits. During the period of maximal antibody accumulation (10 weeks) the titer ranged from 1:16 to 1:128. When tested after 5 months these antibodies were found in 20% of cases, in low titer.

Antibodies to 5-HT were found 3-4 weeks after local destruction of the hippocampus in 50% of cases and were detected for 1.5 months of the investigation in most (80%) animals.

After 2 weeks antibodies were found in 12.5% of the experimental animals to heart TA. After 4 weeks these antibodies were found in 75% of cases, and after 6 to 8 weeks, in all animals in maximal titer. Antibodies to lung TA were found in most (69%) animals 4 weeks after hippocampal destruction. After 6 weeks these antibodies were found in 100% of cases. Their titer during this period reached its maximal value. Antibodies to neurotransmitters and TA of the nervous system and viscera could not be detected in the control animals.

Hippocampal destruction thus led to induction of a series of autoimmune responses in the following order of magnitude: antibodies to hippocampal TA, autoantibodies to NA, the heart, and lung. The time course of formation of antibodies to neurotransmitters, on one hand, and to heart and lung TA on the other hand, suggests that the relationship between these immune processes is one of cause and effect. Hippocampal pathology evidently causes a disturbance of the state of the brain neurotransmitter systems and of mediator metabolism, leading to the formation of new antigenic complexes, incorporating neurotransmitters. These antigenic complexes induce synthesis of autoantibodies to regulating factors.

The possibility of induction of an immune response to catecholamines and 5-HT was demonstrated in principle in experiments involving immunization with these haptens, conjugated with carrier proteins [5, 14].

Autoantibodies to several low-molecular-weight physiologically active substances were discovered in [4]. It can be tentatively suggested that induction of synthesis of antibodies to neurotransmitters causes pathology of regulation of visceral functions. Evidence in support of this view is given by previous data showing diminution of the response of the cardiovascular and respiratory systems to intravenous injection of adrenalin [9]. This effect coincides with the period of intensive accumulation of antibodies to catecholamines in the blood and is not found in the stage of lowering of their titer.

It must be pointed out that induction of synthesis of antibodies to neurotransmitters precedes the development of autoimmune responses to visceral TA.

LITERATURE CITED

1. L. V. Devoino and R. Yu. Il'yuchenok, Monoaminergic Systems in Regulation of Immune Responses (Serotonin, Dopamine) [in Russian], Novosibirsk (1983).
2. V. A. Evseev and S. V. Magaeva, Immunopathology of Nervous and Mental Diseases [in Russian], Moscow (L983), pp. 51-53.
3. V. A. Evseev, S. V. Magaeva, and K. D. Pletsityi, Zh. Mikrobiol., No. 5, 114 (1978).
4. A. S. Zaks and A. A. Bykova, Fiziol. Zh. SSSR, No. 9, 1319 (1977).
5. I. E. Kovalev and O.Yu. Polevaya, Biochemical Bases of Immunity to Low-Molecular-Weight Chemical Compounds [in Russian], Moscow (1985).
6. E. A. Korneva and V. A. Shekoyan, Regulation of Defensive Functions of the Organism [in Russian], Leningrad (1982).
7. G. N. Kryzhanovskii, Determinant Structures in the Pathology of the Nervous System [in Russian], Moscow (1980).
8. S. V. Magaeva, "The immunodeficiency state in experimental hippocampal pathology," Author's Abstract of Dissertation for the Degree of Doctor of Biological Sciences (1979).
9. S. V. Magaeva, A. V. Martynenko, and M. V. Martynenko, Problems in Experimental and Clinical Pathology [in Russian], Vol. 6, L'vov (1984), pp. 53-55.
10. O. Yu. Polevaya, L. A. Basharova, and I. E. Kovalev, Khim.-Farm. Zh., No. 7, 32 (1981).
11. A. I. Polyak, Higher Brain Functions Under Normal and Pathological Conditions [in Russian], Leningrad (1979), pp. 133-141.
12. H. O. Besedovsky and E. Sorkin, Psychoneuroimmunology, E. Adler, ed., New York (1981), pp. 545-571.
13. B. D. Jankovic and K. Isakovic, Int. Arch. Allergy, 43, 360 (1973).
14. R. A. O'Brien, M. Boublik, and S. Spector, J. Pharmacol. Exp. Ther., 194, 145 (1975).
15. C. H. Sawyer, J. W. Everett, and J. Green, J. Comp. Neurol., 101, 801 (1954).

EFFECTIVENESS OF EXTRACORPOREAL MEMBRANE OXYGENATION IN ANIMALS WITH ACUTE RESPIRATORY FAILURE

I. E. Trubina, A. A. Bozh'ev, M. Sh. Avrushchenko, V. T. Gorun, and Z. R. Karichev

UDC 616.24-008.64-036.11-092.9-085.835-036.8-07

KEY WORDS: extracorporeal membrane oxygenation; acute respiratory failure; hemodynamics; oxygen transport.

Of all the pathophysiological aspects of the use of extracorporeal oxygenation in the combined treatment of acute respiratory failure when artificial ventilation of the lungs (AVL) proves ineffective, the greatest attention has been paid to gas exchange [2-5, 7, 9]. Changes in the circulatory system accompanying the method of extrapulmonary oxygenation, which are no less important in determining the oxygen supply to the body, have not been systematically studied, and fragmentary information on this matter can be found only in isolated publications [6, 8, 9].

The aim of the present investigation was to study the state of the central hemodynamics, gas exchange, and oxygen transport in animals with marked hypoventilation during the period of extracorporeal membrane oxygenation using different methods of perfusion.

Institute of General Resuscitation, Academy of Medical Sciences of the USSR. Department of Emergency Heart Surgery, Central Research Institute of Hematology and Blood Transfusion, Ministry of Health of the USSR, Moscow.

(Presented by Academician of the Academy of Medical Sciences of the USSR V. A. Negovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 102, No. 7, pp. 12-14, July, 1986. Original article submitted June 14, 1985.

0007-4888/86/0007-0880$12.50