EFFECT OF CENTRAL CHOLINOLYTICS ON THE PRIMARY IMMUNE RESPONSE IN RABBITS

B. A. Marat

UDC 615.217.34.015.46 : 612.017.1

The effect of central muscarinic and nicotinic cholinolytics on the formation of complement-fixing antibodies was investigated. It was shown that α-methylamizil (IEM-275),* a compound with mainly central muscarinic cholinolytic activity, does not affect this process; β-ethyldifacil (IEM-506),† a compound with marked nicotinic cholinolytic action, stimulates the primary immune response. These results suggest that central nicotinic cholinergic structures are among the functional components of the central system of response to an antigen.

It has now been proved that the CNS has a modulating effect on immunological processes [1, 2, 7, 17]. By acting on individual structures of CNS in neurophysiological experiments, it is possible to modify the course of immunological reactions [11, 18] and, in particular, the process of antibody formation [9, 10, 19].

A possible approach to the study of the mechanisms of central control over the reaction of the body to an antigen is by the use of a pharmacological agent, and this course is particularly relevant at the present time in connection with prospects for the use of drugs acting on the CNS to produce deliberate changes in the intensity of immunological processes. In recent years several pharmacological compounds acting predominantly on the CNS, and classified by Anichkov [5] as central cholinolytics, have been synthesized.

In the investigation described below the effects on complement-fixing antibody formation by the following central cholinolytics were studied: the preparation IEM-275 (α-methylamizil; AMA), with marked muscarinic cholinolytic activity; and the preparation IEM-506 (β-ethyldifacil; BED), with marked nicotinic cholinolytic activity.

EXPERIMENTAL METHOD

Forty chinchilla rabbits weighing 2-3 kg were used. The animals were immunized with a single intravenous injection of horse serum, heated to 56°C, in a dose of 0.25 ml/kg body weight. Blood samples were taken before immunization and on the 4th, 5th, 7th, 8th, 10th, 14th, 21st, and 25th days after injection of the antigen. Administration of the pharmacological agents was started two days before immunization, by the following schemes: series I (six rabbits) – AMA injected intravenously in a dose of 1 mg/kg daily for 15 days; series II (eight rabbits) – AMA injected subcutaneously in a dose of 2 mg/kg daily for 15 days; series III (six rabbits) – BED injected intravenously in a dose of 5 mg/kg daily for five days. Since BED, when injected parenterally, has a strong irritant action on the tissues at the site of injection, and repeated injections lead to the formation of considerable edema, in the experiments of series IV (10 rabbits), an aqueous 1.5% solution of BED was given by mouth through a tube in a dose of 20 mg/kg daily for 15 days. Both drugs were given in doses causing significant changes in the character of processes taking place in the structures of the CNS [6, 12, 13]. In the experiments of series V (control, 10 rabbits) physiological saline was given to the animals (intravenously, subcutaneously, or by mouth) daily for 15 days. The anti-

* The α-methyl derivative of benactyzine – Translator.

† The β-ethyl derivative of adiphenine – Translator.

Department of General Pathology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 76, No. 8, pp. 97-99, August, 1973. Original article submitted May 22, 1972.

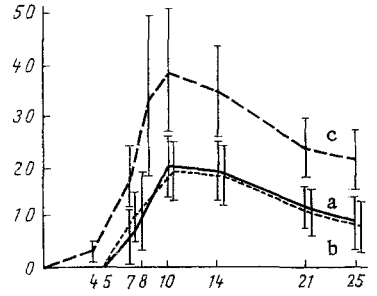

Fig. 1. Dynamics of antibody production in control rabbits (a) and in rabbits receiving AMA (b) and BED (c). Abscissa, days after immunization; ordinate, reciprocals of antibody titers.

body titers were determined by the long-term complement- fixation test in the cold [8].

EXPERIMENTAL RESULTS

Before the injection of horse serum, no antibodies against this antigen were found in any of the 40 rabbits used in the experiments. The intensity and dynamics of the immune response in the rabbits of series V (control) were basically similar in type. Antibodies were first discovered on the 7th day after immunization, and by the 10th day their titer had reached its maximum, which was followed by a very slight decrease to the 14th day and then a faster, steady decrease in the blood antibody level (Fig. 1a).

When injected both intravenously (series I) and subcutaneously (series II), AMA had no effect on the intensity or dynamics of the immune response. The curve reflecting antibody formation in the rabbits of series I and II (Fig. 1b) was completely identical with the curve of antibody formation in the rabbits of the control series (Fig. 1a).

Intravenous injection of BED changed the intensity and dynamics of the immune response in the rabbits of series III. Antibodies were now found on the fourth day after immunization; the highest titer was observed (just as in the rabbits of series V, I, and II) on the 10th day, but the titers themselves were considerably higher. After the 10th day the antibody titer fell gradually but still remained higher than in the rabbits of series V, I, and II.

As was pointed out above, parenteral injection of BED led to edema and inflammatory changes at the site of injection. To rule out the possibility of a nonspecific immunological reaction connected with the inflammatory changes in the tissues, BED was given to the rabbits of series IV by mouth in a dilute aqueous solution. The mucous membrane of the stomach and small intestine of two rabbits from series IV was subjected to pathological investigation on the 16th day after the beginning of BED administration. No signs of inflammation were found.

Since the intensity and dynamics of antibody formation were identical in the rabbits of series III and IV, despite differences in the duration and method of administration of the compound, the results of series III and IV are considered together (Fig. 1c).

This investigation thus showed that AMA, with predominantly central muscarinic cholinolytic activity, does not affect the formation of complement-fixing antibodies; BED, a substance with marked central nicotinic cholinolytic activity, modifies the primary immune response (causes antibodies to appear relatively earlier in the blood, and to reach a higher titer in the blood than in animals of the control series).

These results suggest that central nicotinic cholinergic structures are among the functional components of the system for neuro-humoral regulation of the reaction of the body to antigen, along with adrenergic and serotoninergic structures [3, 4].

The pathways whereby the CNS exerts its modulating influence on immunological processes are not yet sufficiently clear. One possibility is a humoral mechanism, in which information is transmitted through various biochemically active substances, including hormones [7, 21].

Central cholinolytics, by acting on cholinergic structures of the hypothalamo-hypophyseal system, may influence the adrenal function of the adrenal glands [14] and modify the blood corticosteroid level [20]. Pharmacological agents with marked nicotinic cholinolytic properties, by blocking cholinergic structures of the hypothalamo-hypophyseal system, can increase adrenocortical activity, whereas the blocking of central muscarinic cholinergic systems is reflected to a lesser degree in adreno-cortical activity [15, 16].

The possibility that BED may act directly on the immunocompetent cells cannot be ruled out, although no indication could be found in the periodical literature to suggest that this substance has any effect on lymphoid tissue.

The further study of the mechanisms of central modulation of immunological processes by the use of pharmacological agents acting on particular biochemical mediator systems of the brain is a promising method of investigating ways of deliberately modifying the intensity of these reactions.

LITERATURE CITED

1. A. D. Adko, Klin. Med., No. 12, 3 (1959).
2. N. V. Vasil'ev, The Role of the Nervous System in Infection and Immunity [in Russian], Tomsk (1963).
3. L. V. Devoino, in: Collected Transactions of the Third Scientific Conference of Physiologists, Biochemists, and Pharmacologists of the Western Siberian Union [in Russian], Tomsk (1965), p. 290.
4. L. V. Devoino, A Study of the Role of Serotonin in the Formation of Immune Reactions, Author's Abstract of Doctoral Dissertation, Ryazan' (1972).
5. P. P. Denisenko, in: Abstracts of Proceedings of Symposia at the Ninth Congress of the All-Union Society of Physiologists, Biochemists, and Pharmacologists [in Russian], No. 3, Minsk (1959), p. 209.
6. P. P. Denisenko, The Central Cholinolytics [in Russian], Leningrad (1965).
7. P. F. Zdrodovskii, Problems in Infection, Immunity, and Allergy [in Russian], Moscow (1963).
8. V. I. Ioffe and K. M. Rozental', Zh. Mikrobiol., No. 12, 65 (1943).
9. E. A. Korneva and L. M. Khai, Fiziol. Zh. SSSR, No. 1, 42 (1963).
10. E. A. Korneva and L. M. Khai, Abstracts of Proceedings of the First All-Union Conference on the Physiology of the Autonomic Nervous System and Cerebellum [in Russian], Erevan (1964), p. 352.
11. E. A. Korneva, R. P. Ogurtsov, Yu. N. Zubzhitskii, et al., Dokl. Akad. Nauk SSSR, 186, No. 1, 215 (1969).
12. V. A. Krauz, Comparative Characteristics of the Action of Certain Central Muscarinic and Nicotinic Cholinolytics on Various Structures and Systems of the Brain, Author's Abstract of Candidate's Dissertation, Leningrad (1969).
13. N. A. Losev, Pharmacological Analysis of α- and β-Derivatives of Amizil and Spasmolytin, Author's Abstract of Candidate's Dissertation, Leningrad (1968).
14. E. I. Malygina, in: The Pharmacology of New Sedatives and Their Clinical Application [in Russian], Leningrad (1962), p. 134.
15. A. N. Poskalenko, Probl. Éndokrinol., No. 4, 14 (1960).
16. A. N. Poskalenko, in: The Pharmacology of New Sedatives and Their Clinical Application [in Russian], Leningrad (1962), p. 129.
17. L. M. Rumbesht, in: Mechanisms of Some Pathological Processes [in Russian], No. 3, Rostov-on-Don (1970), p. 363.
18. V. Ya. Solov'ev, Participation of the Posterior Nuclei of the Hypothalamus in Mechanisms of Rejection of Skin Homografts, Author's Abstract of Candidate's Dissertation, Saratov (1968).
19. L. M. Khai, M. V. Kovalenkova, E. A. Korneva, et al., Zh. Mikrobiol., No. 10, 7 (1964).
20. S. V. Anichkov, A. N. Poskalenko, and V. E. Ryzhenkov, in: First International Pharmacological Meeting, Proceedings, Vol. 1, Prague (1963), p. 1.
21. W. Pierpaoli, C. Baroni, and N. Fabris, et al., Immunology, 16, 217 (1969).