DYNAMICS OF THE FUNCTIONAL STATE OF SKIN RECEPTOR ENDINGS AFTER BCG VACCINATION

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Immunization of rabbits with BCG vaccine caused changes in the physiological state of the skin receptors. These changes differed in direction depending on the stage of the vaccination process and the location of the receptor zone relative to the vaccinal focus.
KEY WORDS: BCG vaccine; skin receptors; functional activity.

Widely different levels of the nervous system, including its peripheral afferent division, the receptor endings, have been shown to participate in the pathogenesis and immunogenesis of tuberculosis [6, 7, 10-14, 17]. However, an analysis of the literature on this problem showed that much still remains unexplained and requires further study. In particular, no reference could be found to any systematic study, at the different phases of the immunological changes, of the functional state of the receptor system following vaccination with bacillus Calmette-Guerin (BCG).

The object of this investigation was to study the dynamics of the functional state of the skin receptor endings and its correlation with changes in various indices of immunological reactivity followed BCG vaccination.

EXPERIMENTAL METHOD

Experiments were carried out on 69 rabbits weighing 2.5-3 kg, of which 57 animals were vaccinated and the other 12 remained intact. Bacillus Calmette-Guerin vaccine (1 mg) was injected subcutaneously into the rabbits in the region of the right knee joint (in five rabbits, in the region of the right half of the thorax). The immunized animals took part in the experiments between the 1st and 150th days after vaccination.

In acute experiments under urethane anesthesia (0.9 g/kg, intramuscularly) afferent impulses were recorded from the genicular branches of the saphenous nerve in both hind limbs. The potentials were amplified by the UBPI-02 ac amplifier and recorded on the MPO-2 loop oscillograph. After spontaneous unit activity had been recorded for 30 sec, the test substances, namely physiological saline, potassium chloride solution (30 mM), and a solution of purified whole tuberculin, were injected in a volume of 0.2 ml intradermally into the area of skin innervated by the genicular branch of the saphenous nerve. Activity evoked by these substances was recorded during the first 10 and 30 sec, and 1, 5, and 10 min after injection. The number of spokes was counted visually and the numerical results were subjected to statistical analysis by Student's method.

Changes in general immunological reactivity of the animals were assessed by the Mantoux test (1:10) and also from the macroscopic and microscopic development of the primary vaccinal focus.

EXPERIMENTAL RESULTS

The experimental results showed that purified tuberculin, on contact with the receptor endings of the skin of the unvaccinated rabbits, caused no significant change in spontaneous activity in the sensory fibers of the cutaneous nerves (Fig. 1). Injection of potassium chloride caused a marked increase in the flow of afferent impulses in the fibers innervating the test zones under the same conditions (Fig. 2). During the immunological response the character of the spike discharge in response to injection of specific and nonspecific stimuli into the test zone changed.

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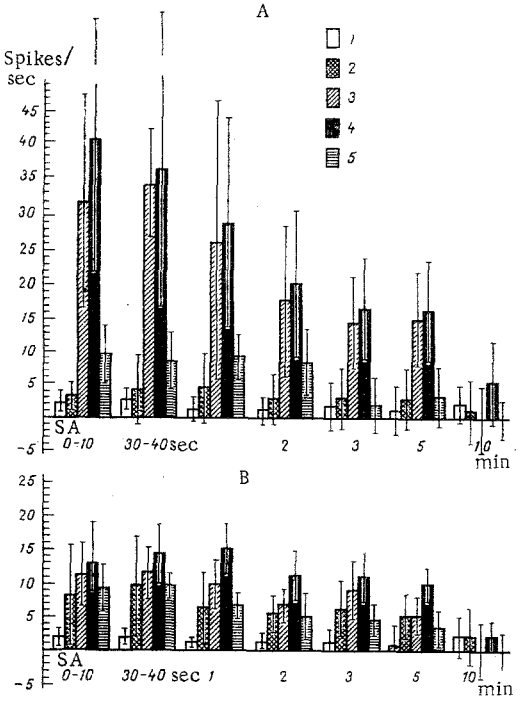

Fig. 1. Effect of tuberculin on flow of afferent impulses in regional nerve. A) Region of skin around primary vaccinal focus; B) region of skin on symmetrical limb relative to primary vaccinal focus in rabbit. 1) Intact rabbit; 2, 3, 4, 5) vaccinated rabbits on 1st-10th, 10th-30th, 30th-60th, and 100th-150th days, respectively, after vaccination. Abscissa, time after injection of tuberculin; ordinate, increase in afferent discharge (in spikes/sec). SA) Spontaneous activity.

In the first period after BCG vaccination (1st-10th days) a clear tendency was observed for the level of evoked afferent activity after injection of tuberculin and potassium chloride to exceed that in the intact animals. This increase was observed to a greater or lesser degree in all receptor zones studied (see Figs. 1 and 2). During the development of the postvaccinal response (10th-60th days) a further increase was observed in the evoked afferent discharge recorded from the regional cutaneous nerves after injection of tuberculin (Fig. 1). The maximal response of the receptors of the skin region to tuberculin was observed on the 30th-60th days after BCG vaccination. When potassium chloride was injected on the 10th-60th days after immunization the changes in the afferent flow differed in direction depending on into which of the receptor zones it was injected. The response of receptor endings in the skin close to the primary vaccinal focus to potassium chloride increased in intensity with the development of the vaccinal process parallel with the response to tuberculin. In other areas of skin the sensitivity of the receptor endings to potassium chloride was reduced. The most marked decrease was observed in the period from 10 to 30 days after vaccination (Fig. 2). The decrease in the response of the skin receptors to tuberculin took place on the 100th-150th days. The injection of potassium chloride into all the skin zones tested on the 100th-150th days after immunization caused a response which differed only slightly from that of the intact animals.

The Mantoux test became positive starting from the 10th-12th days after immunization. Its intensity reached a maximum on the 30th-60th days after vaccination and fell toward the 100th-150th days after vaccination. The development of the focus of specific inflammation ended on average by the 30th-45th days (Fig. 3).

When the results are analyzed it must be remembered that the increase in the flow of afferent impulses in response to potassium chloride reflects chiefly the functional state of the receptor endings themselves [16, 19, 20], whereas mainly the cellular changes in the surrounding tissues are revealed by the action of tuberculin

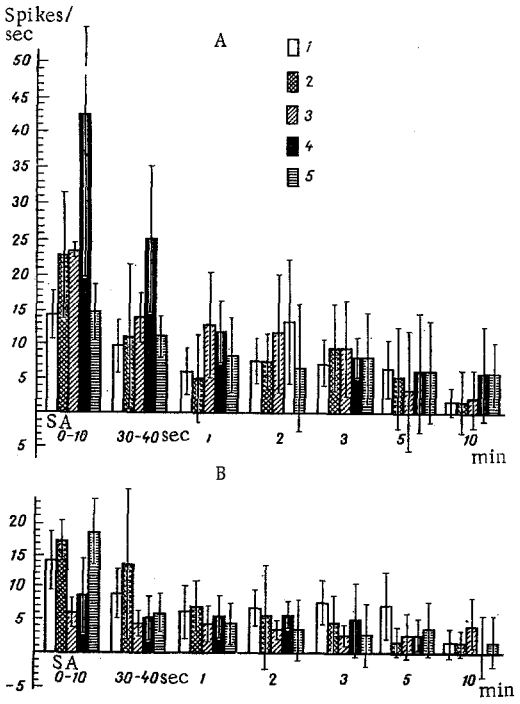

Fig. 2. Effect of potassium chloride on afferent spike flow in regional nerve. Abscissa, time after injection of potassium chloride. Remainder of legend as in Fig. 1.

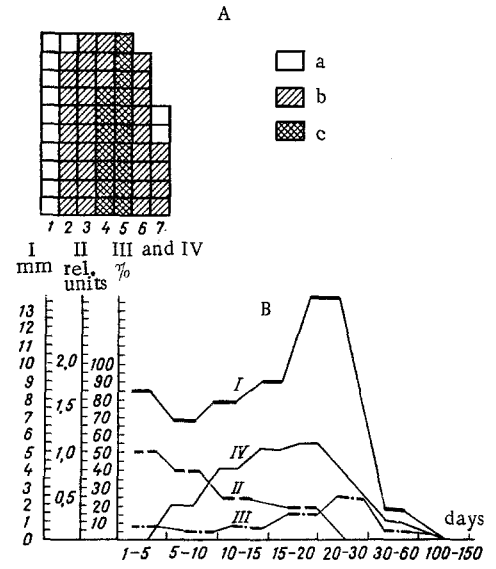

Fig. 3. Dynamics of development of Mantoux test (A) and of primary vaccinal focus (B) in rabbits immunized with BCG vaccine. A: 1, 2, 3, 4, 5, 6, and 7) 5, 12, 16, 20, 30, 60, and 100 days, respectively, after vaccination. a) Mantoux test negative; b) Mantoux test positive (diameter of papule 1-1.5 cm); c) Mantoux test strongly positive (diameter of papule 1.5-3 cm). Each square represents one rabbit. B: Abscissa, time after BCG vaccination (in days); ordinate: I) diameter of area of infiltration (in mm); II) hyperemia (in relative units); III and IV) necrosis and ulceration respectively (in %).

[15]. It can accordingly be concluded that, depending on the period of the vaccination process and the relationship of the receptor zone to the primary vaccinal focus, the changes in the functional state of the skin receptors will differ in direction and intensity, whereas the change in reactivity of the cells surrounding them will be in the same direction but of varied intensity. Comparison of the dynamics of the changes observed with the development of the specific immunological response suggests that in the initial period of immunization (1st-10th days) the nonspecific harmful action of BCG predominates. In the 10th-60th days after immunization these changes are evidently not only the result of the toxic action of the vaccine, but they also depend on changes in the tissues and also, perhaps, in the receptor endings themselves, brought about by the development of the specific immunological response of the animal. It must be emphasized that, regardless of whether the changes in functional activity of the receptors are the result of the harmful action of BCG vaccine or of the specific immunological response of the animal, they are ultimately the result of the participation of receptors in the nonspecific response of the nervous system directed toward the regulation of the processes maintaining homeostasis when disturbed by the vaccine.

This conclusion is in agreement with investigations by workers who consider that the primary point of application of bacterial antigens is the tissue, and that the contribution of the nervous system is merely to regulate the strength and intensity of the specific responses [8, 9]; they likewise do not contradict the results of investigations showing changes in the sensitivity of the receptors to the action of antigens in the course of the immunological response [1-4].

It can be concluded from a comparison of the direction of the change in the functional state of the skin receptors and the reactivity of the tissues, and also data in the literature showing that any "extremal" stimulus not only evokes pathological responses but also, at the same time, activates the mechanisms of compensation [5, 18], suggests that at the level of the receptor apparatus an adaptive mechanism ensuring more effective functioning of the CNS under conditions of antigenic stimulation is activated. The aim of this mechanism, which also functions at other levels of the nervous system [18], is to limit the supply of excess information to higher levels of the brain. In response to stronger antigenic stimulation, for example, in the region of the primary vaccinal focus, and also after injection of tuberculin into the receptor zones, giving rise to sharp biochemical changes in the tissues of the immunized animal, the processes of correction of the spike flow at this particular level of the nervous system are evidently inadequate.

LITERATURE CITED

1. A. D. Ado, Antigens as Extremal Stimuli of the Nervous System [in Russian], Moscow (1952).
2. A. D. Ado (editor), The Mechanisms of Action of Microorganisms on the Nervous System [in Russian], Moscow (1957).
3. A. D. Ado (editor), Problems in the Pathological Physiology of Infection [in Russian], Moscow (1962).
4. A. D. Ado, General Allergology (A Textbook for Doctors) [in Russian], Moscow (1970).
5. P. K. Anokhin (editor), The Problem of Center and Periphery in the Physiology of Nervous Activity [in Russian], Moscow (1935).
6. I. M. Bondarev, "The pathogenesis of the experimental tuberculous cavity of the lung in dogs," Author's Abstract of Candidate's Dissertation, Rostov-on-Don (1963).
7. I. M. Bondarev, in: The Pathogenesis and Healing of Focal and Destructive Forms of Tuberculosis [in Russian], Moscow (1967), pp. 7-22.
8. P. F. Zdrodovskii, Problems of Infection and Immunity [in Russian], Moscow (1961).
9. P. F. Zdrodovskii, Problems in Infection, Immunity and Allergy [in Russian], Moscow (1969).
10. G. S. Kan, in: The Study of the Role of the Nervous System in the Pathogenesis, Immunogenesis, and Treatment of Tuberculosis [in Russian], No. 1, Moscow (1954), pp. 51-58.
11. G. S. Kan, The Nervous System and Tuberculosis [in Russian], Leningrad (1955).
12. G. S. Kan, in: The Study of the Role of the Nervous System in the Pathogenesis, Immunogenesis, and Treatment of Tuberculosis [in Russian], No. 2, Moscow (1961), pp. 243-255.
13. G. S. Kan, in: Collection of Authors' Abstracts of a Scientific Review Session of Leningrad Institute of Tuberculosis [in Russian], Leningrad (1968), pp. 49-50.
14. G. S. Kan, in: Mechanisms of Regulation of Physiological Functions [in Russian], Leningrad (1971), pp 185-192.
15. G. I. Kositskii and V. M. Smirnov, The Nervous System and Stress [in Russian], Moscow (1970),
16. V. A. Lebedeva, Mechanisms of Chemoreception [in Russian], Moscow–Leningrad (1965).
17. A. D. Semenov, Pulmonary Tuberculosis [in Russian], Leningrad (1963).

18. S. I. Frankshtein, in: Current Problems in the Physiology and Pathology of the Nervous System [in Russian], Moscow (1965), pp. 152-164.
19. V. N. Chernigovskii, Afferent Systems of the Internal Organs [in Russian], Kirov (1943).
20. V. N. Chernigovskii, Interoceptors [in Russian], Moscow (1960).

POTENTIATING ACTION OF METABOLIC PRODUCTS OF BLOOD LYMPHOCYTES ON POLYMORPH VULNERABILITY

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The supernatant obtained after culture of sensitized blood lymphocytes with an appropriate allergen (tuberculin) potentiates injury to polymorphs (V. A. Fradkin's index of blood neutrophil injury).
KEY WORDS: lymphocytes; polymorphs, allergy.

Until recently comparatively little attention had been paid to the study of the role of polymorphonuclear leukocytes in the development of immunity and of specific sensitization.

It was shown in the 1950s that the blood neutrophils can be modified and destroyed by the action of a specific antigen–antibody complex [4, 7]. On this basis, granulocytic diagnostic tests began to be used in allergology, including the NII (blood neutrophil injury index in vitro) test suggested by Fradkin in 1962. It was later shown [1, 2] that the mechanism of the NII test falls into the category of tests with target cells to an antigen–antibody complex.

The attention of immunologists is nowadays drawn not only to the migration of polymorphs from the bloodstream, the phagocytosis of immune complexes, and liberation of mediators, but also to humoral complement-dependent factors of neutrophil chemotaxis [5]. Papers were published in which the effect of neutrophils was examined on the level of specific responses of the blood lymphocytes such as the blast-formation phenomenon [3].

The object of this investigation was to study the effect of metabolic products of lymphocytes, transferred into liquid medium during culture of mononuclear cells in vitro, on the ameboid reaction of the blood neutrophils. The starting point was the known fact [6] that during culture of cells of lymph nodes of a sensitized guinea pig in the presence of antigen a factor with a cytotoxic action on the other elements passes into the supernatant.

EXPERIMENTAL METHOD AND RESULTS

The action of the supernatant on the intensity of ameboid activity of the blood neutrophils was studied by the NII test on 53 patients aged from 17 to 45 years with various forms of pulmonary tuberculosis, predominantly in the phase of activation of the disease. The response of the blood neutrophils was assessed in full accordance with the conditions of the NII test as described by Fradkin.

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