ENDOCRINE FUNCTION OF APUD CELLS OF IMMUNOCOMPETENT ORGANS IN SOME FORMS OF IMMUNE RESPONSE

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Research workers are currently paying great attention to the concept put forward by Pearse [14] that there exists in the body a specialized system of cells (the APUD system) which, being distributed among practically all the vitally important organs, is directly concerned in the maintenance of homeostasis at the organ level through the production of biogenic amines and peptide hormones. Immunocompetent organs are known to contain cells which, in their histochemical and immunohistochemical properties can be classed in the APUD system [4, 5]; the spectrum of the biologically active substances produced in the organs of immunity appears to be as follows: thymus — serotonin, melatonin, and catecholamines; bone marrow — serotonin, melatonin, and somatotrophic hormone (STH); spleen — histamine, serotonin; lymph nodes — histamine.

This paper describes an attempt to establish changes in the endocrine function of the APUD cells of immunocompetent organs during various forms of immune response and to assess the possible self-regulatory relations between the APUD system and the immunity system — the two most important systems controlling homeostasis.

EXPERIMENTAL METHOD

The experimental material consisted of thymus, bone marrow, spleen, and lymph nodes obtained from rabbits and guinea pigs. Tests were carried out both on intact animals (control) and in the course of immunization. Rabbits were immunized by intraperitoneal injection of heated typhoid vaccine in a dose of 3 ml and were reimmunized 4 months later. The rabbits were killed 3 days after primary immunization and the same number of days after the second injection of vaccine. One of the schemes of immunization envisaged the creation of a model of immediate-type hypersensitivity in guinea pigs as suggested by Beklemishev and Sukhodoeva [2], and based on giving two injections, at intervals of 3 days, of sonicated antigen from a suspension of a vaccine strain of brucellas in Freund's incomplete adjuvant. The guinea pigs were killed on the 14th day of sensitization. Sections of the organs were stained with hematoxylin and eosin and by the histochemical methods of Sevki, Masson, and Dominici. Immunochemical tests also were carried out with antisera against serotonin, melatonin, and STH. In the microscopic study the number of APUD cells was counted in ten fields of vision and the mean number of the corresponding cells was then calculated per field of vision under a magnification of 120. The results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

In the course of the primary immune response the number of APUD cells containing serotonin fell statistically significantly in the thymus and spleen: from 5.12 ± 0.08 cells per field of vision to 0.9 ± 0.12 in the thymus ($P = 0.001$) and from 17.42 ± 0.19 cells per field of vision to 6.53 ± 0.15 in the spleen ($P = 0.001$), reflecting the ability of serotonin to inhibit cell proliferation [9]. In the secondary immune response the number of serotonin-containing APUD cells increased again (up to 6.2 ± 0.1 cells per field of vision). The fall in the number of serotonin-containing cells was even more intensive during sensitization accompanying the development of immediate-type hypersensitivity. This was particularly true of

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APUD cells in the spleen. In the experimental model of this state in the spleen a sharp decrease was observed in the number of serotonin-containing cells (to 0.12 ± 0.01 per field of vision). Perhaps such a distinctive response of the APUD cells is one of the pathogenetic factors concerned in the development of immediate-type hypersensitivity, for one of the mechanisms accompanying the action of serotonin on immunocompetent organs has been shown to be its ability to stimulate the T- and B-suppressor effect [3]. Very probably it is this feature of the immunosuppressor action of serotonin which is expressed in the increase in the number of serotonin-containing cells during the secondary immune response. In cases when, for some reason or other, this type of mechanism does not operate, the conditions are created for the development of an allergic state. As regards melatonin, to interpret the fluctuations in its level it must be recalled that the chief precursor of this hormone in the course of its synthesis is serotonin [13]. From this standpoint it will be clear that the dynamics of the melatonin content in APUD cells of immunocompetent organs in the course of immunization reflects the fluctuation in the numbers of serotonin-containing cells, but the differences in this case were not statistically significant: In the thymus before immunization there were 4.95 ± 0.2 melatonin-containing cells per field of vision, with 4.7 ± 0.01 cells per field of vision during the primary immune response (P = 0.628); APUD cells with melatonin were found in the bone marrow only before immunization.

During the primary immune response a marked increase was found in the number of catecholamine-containing cells in the thymus — from 1.83 ± 0.15 to 12.82 ± 0.06 per field of vision (P = 0.001). Injection of the antigen into the animals caused the appearance of cells of this kind in the spleen also (1.82 ± 0.07 per field of vision); the sensitization process was accompanied by significantly lower activity of the corresponding APUD cells in the spleen — 0.8 ± 0.01 cell per field of vision (P = 0.001). In the course of the secondary immune response the number of catecholamine containing APUD cells in the thymus was practically the same as their initial number before immunzation. A few cells of this kind appeared during the primary immune response in the bone marrow also (0.74 ± 0.04 per field of vision). According to data in the literature, participation of catecholamines in the immune responses of the animal is linked both with the activation of phagocytosis [6] and with direct action on lymphocytes, manifested as the more intensive proliferation of T lymphocytes and an increase in the number of antibody-forming cells [12]. Particular importance is attached to the stimulating action of catecholamines on the primary immune response [15], in full agreement with our own data.

Histamine was found mainly in APUD cells of the peripheral organs of immunity in intact animals. In the course of immunization histamine-containing cells were recorded in the thymus during the primary immune response, but in small numbers (0.75 ± 0.05 per field of vision). Insufficient data have yet been obtained to come down in support of one of the two existing conflicting points of view on the role of histamine in immunogenesis: There is evidence that an increase in histamine production coincides with intensification of blast transformation of lymphocytes [1] and with the development of the productive phase of immunogenesis [10]; meanwhile the possibility that histamine may inhibit immunogenesis through mobilization of serotonin from the depots [7] and also through activation of T suppressors [8] has been mentioned.

STH was found in intact animals only in the APUD cells of the bone marrow; during immunization cells containing this hormone also were recorded in the thymus, bone marrow, and spleen (2, 9, and 3.2 cells per field of vision). According to data in the literature, STH potentiates chiefly T-cell effects, and so reduces T-suppressor activity [11]. The presence of STH in the bone marrow even of intact animals suggests that the role of this hormone in the immune process is not confined to its action on the T-cell system of immunity.

The investigation showed that, besides immunologic mechanisms proper, an important role in the formation of the various forms of immune response is played by a change in the endocrine function of the APUD cells of immunocompetent organs. A further study of self-regulatory relations between the APUD system and the immunity system will present wide opportunities for the understanding of the mechanisms of homeostasis under normal and pathological conditions.

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