EFFECT OF ANTIHISTAMINE DRUGS ON DISEASE IN RATS CAUSED BY ADJUVANT OF THE FREUND TYPE

V. I. Sidorkin and S. I. Kharlampovich

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The antihistaminics dimebolin and compound TVE-80, if injected into rats with a disease caused by administration of adjuvant of the Freund type, depress the inflammatory changes, and facilitate development of productive inflammation with signs of fibrosis of specific granulomas.

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Among the biologically active substances liberated as a result of the antigen–antibody reaction, considerable importance is attached to histamine [4, 5], the activity of which is associated with disturbances of the regional circulation, vascular permeability, and tissue edema [3, 6, 7]. The study of the effect of antihistaminics on the course of diseases the pathogenesis of which is based on autoimmune processes is of considerable interest. In experimental work such a disease is frequently reproduced by injecting Freund's adjuvant into animals [1, 2].

In the present investigation the effect of certain antihistaminics on inflammatory processes arising after injection of adjuvant of the Freund type was studied.

EXPERIMENTAL METHOD

Experiments were carried out on 64 male August rats weighing 145-155 g. The experimental disease was produced by two intraperitoneal injections of 0.5 ml adjuvant at an interval of ten days. The adjuvant consisted of a sterile mixture of 20 mg heat-killed BCG vaccine, 1.5 g lanolin, 2 ml physiological saline, and 8.5 ml mineral oil. The animals were divided into four groups: the rats of group 1 (control) received adjuvant only, the animals of group 2 received adjuvant and dimebolin (2 mg/kg), the rats of group 3 received adjuvant and compound TVE-80 (1 mg/kg) and those of group 4 were healthy intact rats. The compounds were injected as aqueous solutions into the stomach (series I) and intraperitoneally (series II). During the period of observation (50 days) every day the animals were weighed, their rectal temperature was measured at the same time of day, and their general condition was noted. At the end of this period the rats were sacrificed and autopsied, the internal organs (heart, kidneys, adrenals, and liver) were weighed, and material was taken for histological investigation (lungs, liver, spleen, mesenteric glands, small intestine). The tissues were fixed in 10% neutral formalin, dehydrated in alcohols, and embedded in paraffin wax. Sections were stained by Van Gieson's method, with hematoxylin-eosin, and for elastic fibers by Weigert's method.

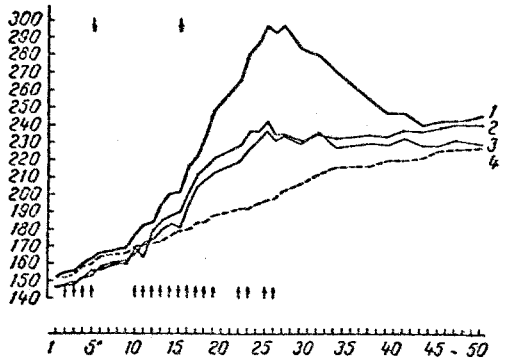

Fig. 1. Changes in weight of rats during disease caused by adjuvant during treatment with dimebolin and compound TVE-80 injected intraperitoneally. Ordinate: weight of animals (in g); abscissa: days of experiment. 1) Control; 2) animals receiving dimebolin; 3) animals receiving TVE-80; 4) healthy animals; ↓) injection of adjuvant; ↑) injection of antihistaminics.

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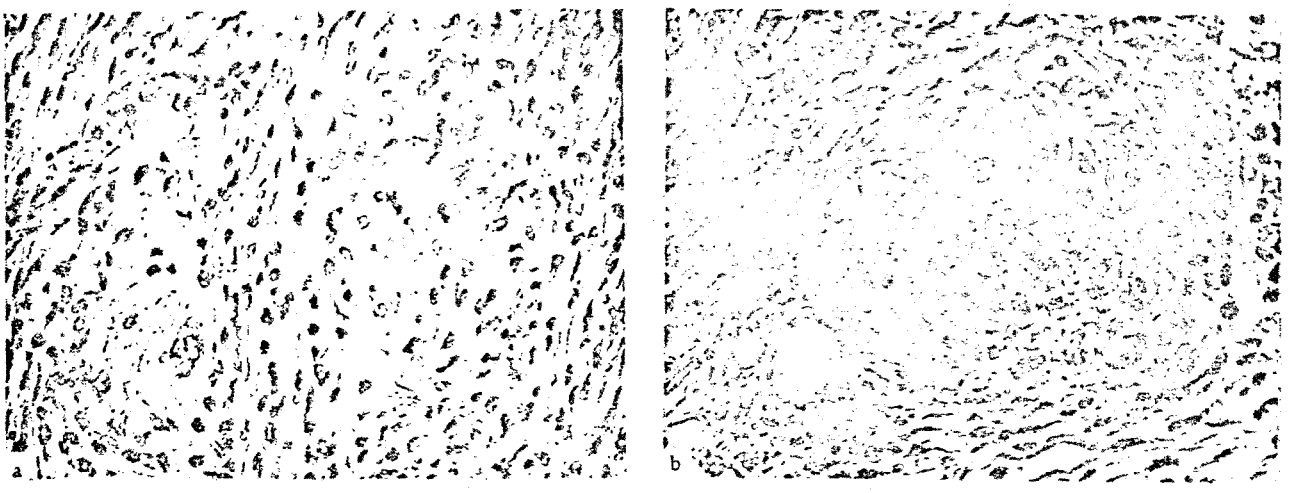

Fig. 2. Granulomas in rats after injection of adjuvant. a) Capsule of liver (control). Two specific granulomas can be seen with lymphocytes and epithelioid cells. In the left part of the figure the center of the granuloma is filled with caseous masses. Hematoxylin-eosin; b) liver capsule of rats receiving compound TVE-80. Productive granuloma with predominance of epithelioid cells. Pirogov–Langhans giant cell in the center. Numerous fibroblasts at the periphery. Van Gieson. Objective 40, ocular 7.

EXPERIMENTAL RESULTS

Injection of adjuvant into the rats in every case produced a disease with the appearance of exudate (ascites) in the abdomen. The development of the disease and the effect of the studied compounds were easily followed from changes in the weight of the animals in the control and experimental groups. The exudate first appeared on the 5th day after the first injection of adjuvant. The process took place more intensively in the animals of the control group and was less marked after injections of compound TVE-80 and dimebolin, regardless of the manner of injection. The difference in the pattern of increase of edema was particularly clear after the second injection of adjuvant (Fig. 1). At the height of the disease, the edema in the animals of the control group was three times greater than in those receiving the test compound. The beneficial effect of these antihistaminics was also shown on the outcome of the edema. The weight of the treated rats became stabilized ten days earlier than the weight of the controls.

No change in body temperature of the rats was observed either after injection of adjuvant or during the action of the test compounds.

No statistically significant difference was found between the weight of the internal organs of the animals belonging to different experimental groups.

At autopsy on the rats of the control group, a large volume of exudate was found in the abdomen of the control group of rats. Tiny grayish yellow nodules were scattered all over the serous membranes. The mesenteric glands, the left border of the liver, the stomach, and the spleen were joined by dense adhesions into a single mass with numerous necrotic foci on its surface.

The results of histological investigation of tissues from organs of the control rats confirmed these observations. In the spleen and lymph glands marked proliferation of lymphoblasts and plasma cells with increased mitotic activity and hyperplasia of the germ centers were observed. Specific granulomas, located on the serous membranes and the capsule of the liver and spleen, consisted of lymphocytes, epithelioid cells, and a few Pirogov–Langhans giant cells. Signs of "fibrinoid swelling" were present in the interstitial tissue. As a rule the center of the granuloma was filled with caseous masses (Fig. 2a).

The macroscopic picture at autopsy on animals of groups 2 and 3 (treated with dimebolin and TVE-80 respectively) was distinguished by the absence of ascites and by a decrease in the number of necrotic nodules on the serous membranes and a smoother appearance of the peritoneum.

Histological examination of tissues of organs from the treated animals showed some difference in the immunomorphological structures compared with the control. In the spleen and lymph glands of animals treated with compound TVE-80, for instance, marked hyperplasia was observed. Numerous polymorpho-

nuclear histiocytes appeared in the pulp, and the germ centers in the follicles were enlarged (because of reticular cells). The specific granulomas found in the spleen, in the capsule of the liver, and in the serous membranes were characterized by numerous epithelioid cells and Pirogov–Langhans giant cells, and also by the comparative rarity of micronecrotic foci. Occasionally fibrous tissue developed around the granulomas (Fig. 2b).

In animals treated with dimebolin the morphological changes demonstrated the more favorable course of the disease. The signs of edema were much less marked in the lymph glands and spleen, and juicy plasma cells were found. In the granulomas which remained, proliferation of epithelioid cells had increased, and at the same time fibrosis was more marked at the periphery. Occasionally granulomas in the stage of leukocytic resorption were seen.

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