ROLE OF α- AND β-ADRENORECEPTORS IN ANAPHYLAXIS OF ISOLATED GUINEA PIG TRACHEA IN AEROSOL ALLERGY TO MITE (Dermatophagoides pteronyssinus) ANTIGEN

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The β-adrenergic concept of the pathogenesis of bronchial asthma [15] is based on a supposed inherited and acquired defect of the β-adrenergic receptors of the bronchopulmonary system [5]. This point of view has subsequently been confirmed by clinical observations [3, 5].

Evidence of the important role of β-adrenoreceptors in the genesis of allergic bronchospasm is also given by the fact that administration of β-adrenolytics to patients with bronchial asthma for treatment of a concomitant disease may lead to a severe attack of bronchial asthma [3, 13]. Contrary opinions have also been expressed. For example, the view has been expressed that β-adrenoreceptor blockade cannot be the cause of development of bronchial asthma and that the primary immunogenic processes initiating development of this disease excite primarily α-adrenoreceptors [14].

By injecting dihydroergotamine (an α-adrenolytic) into sensitized guinea pigs before producing anaphylactic shock, Kozlov [7] obtained potentiation of the anaphylactic shock.

In the present investigation the importance of the functional state of the α- and β-adrenoreceptors in the mechanism of anaphylactic bronchial spasm was studied during aerosol sensitization of animals with dust mite antigen.

EXPERIMENTAL METHOD

Seven series of experiments were carried out on guinea pigs weighing 250-350 g. Animals of series I, II, III, and IV were subjected to aerosol sensitization with a saline extract of dust–mite mixture (50% house dust and 50% mites) in six cycles. On the 14th-15th day after the six cycles of aerosol sensitization, the animals of series II were injected with isoproterenol in a dose of 1 mg/kg body weight 5-6 min before decapitation, the animals of series III were treated with obsidan (propranolol) (1 mg/kg), and the guinea pigs of series IV received dihydroergotamine (1-3 mg/kg). All substances were injected intravenously. The sensitized animals of series I (receiving no drugs) served as the control for the experiments of series II, III, and IV. The intact guinea pigs of series V, VI, and VII also received isoproterenol, obsidan, and dihydroergotamine, respectively, before sacrifice, in the same doses as the experimental animals.

For inhalation sensitization a 10% saline extract of the mite Dermatophagoides pteronyssinus with house dust (8 mg protein/ml) was used. The antigen was prepared and aerosol sensitization of the guinea pigs carried out by the method described by the writer previously [8, 9].

The anaphylactic reaction of the trachea of the animals of series I, II, III, and IV was studied in vitro [12] with determination of $\sqrt{\Delta h}$ (Δh denotes the difference between the levels of Krebs–Henseleit solution in the capillary tube before and after the anaphylactic reaction of the hollow trachea). The reaction of the sensitized isolated trachea to histamine ($4 \cdot 10^{-7}$ g/ml) and adrenalin ($1 \cdot 10^{-7}$ g/ml) was investigated first. The degree of sensitization of the animal was verified by determining antibodies circulating in the blood stream by Boyden's method (passive hemagglutination test, PHT) in the modification described in [4] and by the indirect mast cell degranulation test (IMCDT).

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Adrenergic nerve structures in the bronchopulmonary tissue of the experimental and control guinea pigs of all series of experiments were studied by a luminescence-histochemical method [10, 11]. Staining with polychrome toluidine blue by Unna's method also was used to detect mast cells.

EXPERIMENTAL RESULTS

Investigation of antibodies circulating in the blood stream by the PHT showed a sufficiently high agglutinin titer after four cycles of sensitization, namely 1:120 ± 22.5 (1:64-1:256).

Anaphylactic contraction of the trachea, a smooth muscle organ, in response to the reacting injection of antigen in vitro was significant in character. For instance, the anaphylactic reaction, expressed as $\sqrt{\Delta h}$, was 1.66 ± 0.04 mm, equivalent to 106% of the reaction of the sensitized trachea to the working dose of histamine. If the constrictor response of the trachea to histamine was 1.59 ± 0.06 mm, the dilator response to adrenalin was 1.17 ± 0.07 mm.

Comparison of these results of reactions to different biologically active substances (histamine and adrenalin) with the corresponding data for intact animals shows a significant increase in sensitivity and in the response of the sensitized smooth-muscle organ to histamine ($P < 0.001$), and their decrease in response to adrenalin ($P < 0.001$), in general agreement with data in the literature obtained by sensitization with other antigens [1, 2].

The magnitude of the anaphylactic reaction of the trachea in vitro in animals of series II (receiving isoproterenol) was significantly less than that of the guinea pigs of series I (control). Anaphylactic constriction of the smooth muscle of the trachea, reflected by $\sqrt{\Delta h}$, was 1.03 ± 0.12 mm ($P < 0.001$) compared with 1.66 ± 0.04 mm in the control. The response of the trachea to histamine was indistinguishable from the control values (series I), but the sensitivity and the dilator reaction of the trachea to adrenalin, at 1.5 ± 0.1 mm, were significantly increased.

Injection of the β-adrenoblocker obsidan into guinea pigs of experimental series III caused a regular increase in the anaphylactic reaction of the isolated trachea, to 1.82 ± 0.06 mm ($P < 0.001$). A single injection of obsidan into the sensitized guinea pigs increased the sensitivity and the constrictor reaction of the trachea to histamine ($P < 0.05$) and sharply reduced the dilator effect of adrenalin (−0.33 ± 0.17 mm; $P < 0.001$). The relaxing action of adrenalin in two guinea pigs was absent altogether, and in three guinea pigs there was actually a weak constrictor effect. It is reported in the literature that propranolol hydrochloride (1-5 μg/ml) leads to slight potentiation of the constrictor action of histamine, but does not change the amount of anaphylactic contraction of the smooth muscle organ [6]. However, the authors cited added the drug they were studying directly to the bath containing the organ, which was a different technique from the one we used.

The results of the experiments of series IV, with administration of the α-adrenolytic dihydroergotamine into the sensitized animals, showed that this drug has no significant effect on the level of the anaphylactic reaction of the trachea (1.72 ± 0.07 mm; $P < 0.5$), although a tendency was observed for anaphylactic constriction of the smooth muscle of the trachea to be increased. Dihydroergotamine did not change the reaction of the sensitized isolated trachea to histamine (1.62 ± 0.07 mm), but significantly increased the relaxing action of adrenalin (−1.28 ± 0.001 mm; $P < 0.001$).

A single injection of isoproterenol into the intact animals of series V caused an increase in the content of the free catecholamine fractions in the lung tissue (diffuse emerald green luminescence), and also intensified the luminescence of adrenergic fibers of varied caliber that were revealed. The contours of the nerve fibers appeared indistinct. Monoamine-containing intact mast cells and macrophages, giving emerald green luminescence, also were found.

The lung tissue of the guinea pigs of series VI (injection of obsidan) gave an uneven dull green luminescence, and regions with whitish green fluorescence also were seen. The adrenergic innervation of the bronchi and vessels was clearly outlined and appeared more abundant than normal, but less abundant than in the animals receiving isoproterenol. Degranulating mast cells with pale green and emerald green granules could be seen.

The lung tissue of animals receiving dihydroergotamine (series VII) also showed unequal and uneven luminescence. Some regions gave dull green and emerald green diffuse luminescence. Adrenergic nerve fibers were rare and had indistinct and unclear outlines. The granules of the mast cells gave pale green luminescence, without any signs of degranulation.

Intense diffuse emerald green luminescence of the lung tissue was found in the sensitized animals of the experiments of series II. Numerous large granular adrenergic nerve fibers and plexuses of these fibers were seen in the wall of the bronchi and bronchioles. Mast cells in a state of degranulation were found less frequently in the lung tissue than in the animals of series I. Monoamine-containing macrophages were distinctly visible.

The lung tissue of the sensitized guinea pigs of series III (receiving obsidan) showed extremely irregular luminescence. Regions of dull green and emerald green luminescence were found, probably indicating unequal uptake of catecholamines by the tissue cells. The rapid fading of the emerald green luminescence attracted attention. Adrenergic nerve fibers with sufficiently clear outlines gave less intense luminescence than in the animals of series II. Adrenergic terminals were rarely seen. The impression was obtained that obsidan significantly blocks the uptake of catecholamines by lung tissue cells. In the peribronchial tissue, in the lumen of the bronchioles, and even in the alveoli, degranulating mast cells were frequently seen.

Injection of dihydroergotamine (series IV) induced characteristic changes in the sensitized animals. The lung tissue showed uneven luminescence, mainly dull green or emerald green in color. Individual adrenergic nerve fibers gave extremely pale luminescence and their outlines were indistinct and unclear.

Dihydroergotamine probably had not only an adrenolytic, but also a sympatholytic action.

Consequently, a single pharmacological stimulation of the β-adrenergic receptors of the external respiratory apparatus of guinea pigs sensitized with aerosols of dust-mite extract considerably reduces the degree of anaphylactic reaction of the trachea in vitro, whereas β-adrenorecptor blockade, on the other hand, potentiates it. Pharmacological α-adrenorecptor blockade has no significant effect on the degree of the anaphylactic reaction of the smooth muscle organ.

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