INHIBITION OF PASSIVE CUTANEOUS ANAPHYLAXIS BY DIPEPTIDES

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The action of certain dipeptides (Lα-alanyl-histidine, Lβ-alanyl-histidine, histidyl-leucine, and glycyl-L-histidine) and of histidine itself on passive cutaneous anaphylaxis was studied in guinea pigs. Lβ-alanylhistidine (carnosine) and Lα-alanyl-histidine were found to inhibit passive cutaneous anaphylaxis. Histidyl-leucine, glycyl-histidine, and histidine had no inhibitory action on passive cutaneous anaphylaxis.

KEY WORDS: *passive cutaneous anaphylaxis*; *homocytotropic antibodies*; *dipeptides*.

A few studies of the inhibitory action of peptides on allergic reactions of immediate type have recently been published. The inhibitory effect of pentapeptides on the Prausnitz-Kuestner reaction has been described [2]. According to the available data [6] carnosine inhibits the development of the Arthüs phenomenon in rabbits.

Investigations of the inhibitory action of peptides on allergic reactions of immediate type are potentially valuable in relation to the treatment of allergic diseases [3].

In the investigation described below the inhibitory action of certain dipeptides on passive cutaneous anaphylaxis (PCA) was studied.

EXPERIMENTAL METHOD

Experiments were carried out on 30 albino guinea pigs weighing 200-250 g. Five groups of passively sensitized animals (each consisting of 6 guinea pigs — 3 experimental and 3 control) were tested. In an epilated area of the dorsal region all the animals were given an intradermal injection of 0.1 ml of antiragweed serum, obtained by immunizing guinea pigs with a 5% suspension of ragweed pollen in incomplete adjuvant in a dose of 0.05 ml, by injection into each footpad. Sera with titers of homocytotropic antibodies of 1:128, 1:256, and 1:512 were used in the experiments. Each serum was injected into the recipients in four dilutions, starting with a dilution corresponding to the titers and going on to lower titers (1:256, 1:128, 1:64, 1:32). After 24 h, 0.5 ml ragweed allergen with 0.25 ml of 5% Evans' blue was injected into the experimental guinea pigs. Thirty minutes before injection of the allergen with this dye, the experimental animals were given an intravenous injection of 10 mg of a dipeptide (Lα-alanyl-histidine, Lβ-alanyl-histidine, histidyl-leucine, and glycyl-L-histidine) or of histidine hydrochloride, whereas the control animals received 1 ml of physiological saline. The reaction was regarded as positive if the diameter of the stain reached 4 mm. The titers of the sera were expressed in negative logarithms to base 2. The mean titer of antibodies expressed in logarithms was determined in the animals of the control and experimental groups, and the difference between them reflected the ability of the substances studied to inhibit the PCA reaction. Dipeptides from Reanal, Hungary, were used in the experiments.

EXPERIMENTAL RESULTS

The guinea pigs of group 1, passively sensitized by homologous antiragweed sera, 30 min before injection of the specific allergen with Evans' blue, received an intravenous injection of 10 mg carnosine (Lβ-alanyl-histidine) in a volume of 1 ml, whereas the control animals of this group received 1 ml of physiological saline. The results of the reaction were read 30 min after injection of the allergen with the dye. Four antiragweed sera with titers of 1:128,

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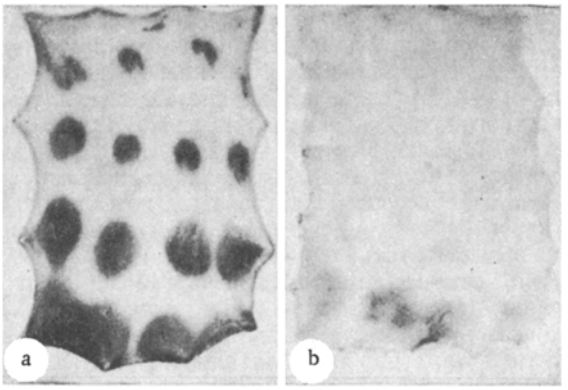

Fig. 1

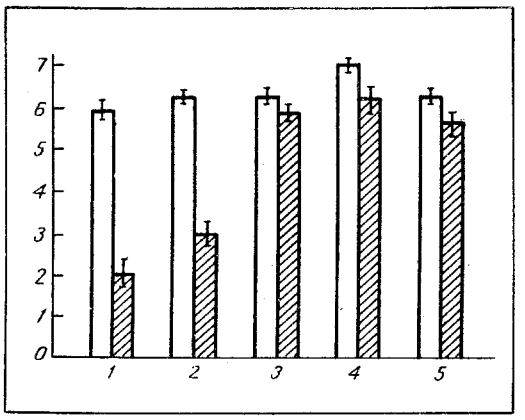

Fig. 2

Fig. 1. Passive cutaneous anaphylaxis: a) control guinea pig; b) experimental guinea pig after injection of 10 mg carnosine.

Fig. 2. Action of dipeptides on passive cutaneous anaphylaxis in guinea pigs. 1) Lβ-alanyl-histidine; 2) Lα-alanyl-histidine; 3) histidyl-leucine; 4) glycyl-L-histidine; 5) histidine. Ordinate, titer of antibodies ($-\log_2$). Unshaded columns) control, shaded columns) experiment.

1:128, 1:256, and 1:256 were tested (Fig. 1). The mean titer of antibodies ($-\log_2$) in the animals of the control group was 5.9 ± 0.3 and in those of the experimental group 2.0 ± 0.57. In animals receiving 10 mg carnosine the PCA reaction was thus depressed, by an amount equal to 3.9 degrees of dilution (Fig. 2, graph 1).

To study its inhibitory action the guinea pigs of group 2 were given an injection of 10 mg Lα-alanyl-histidine. The antibody titer in the control animals of this group was 6.2 ± 0.18 and in the experimental animals 2.9 ± 0.53. Depression of PCA in this group of animals amounted to 3.3 degrees of dilution (Fig. 2, graph 2).

In the animals of group 3 the action of histidyl-leucine was studied. Four antiragweed sera with titers of 1:128, 1:128, 1:512, and 1:512 were injected intradermally into the animals and the experimental animals of the group were given 10 mg histidyl-leucine intravenously. The titer of homocytotropic antibodies in these animals was 5.8 ± 0.12 and in the control animals 6.2 ± 0.1. The difference between the antibody titers in the control and experimental animals of this group was 0.4 (Fig. 2, graph 3).

In the guinea pigs of group 4 the action of glycyl-L-histidine was studied. The animals of this group were passively sensitized with antiragweed sera with titers of 1:256, 1:256, 1:512, and 1:512. The mean antibody titer in the control animals of this group was 7.0 ± 0.16 and in the experimental animals 6.2 ± 0.65. The difference between the titers of the control and experimental animals of this group was 0.8 (Fig. 2, graph 4).

In the animals of group 5 the action of histidine hydrochloride of PCA was investigated. These animals were given four antiragweed sera intradermally: 3 with a titer of 1:256 and 1 with a titer of 1:128. The mean titer of homocytotropic antibodies in the control animals of this group was 6.2 ± 0.15 and in the experimental animals 5.6 ± 0.36. The difference in antibody titers between the control and experimental animals of this group was 0.6 (Fig. 2, graph 5).

The tests thus showed that Lα-alanyl-histidine and Lβ-alanyl-histidine (carnosine) have an inhibitory action of PCA in guinea pigs. The inhibitory effect was strongest in the case of Lβ-alanyl-histidine (carnosine).

Glycyl-histidine, histidyl-leucine, and histidine had no inhibitory action of PCA (Fig. 2).

Homocytotropic guinea pig antibodies are heterogeneous and belong to two classes of immunoglobulins — IgE and IgG_1 [7]. Antibodies belonging to the IgE class are thermolabile, unstable to mercaptoethanol, and they persist in the recipient's skin for 20 days; they sensitize mast cells of guinea pigs [1]. Antibodies of the IgG_2 class are thermostable and resistant to mercaptoethanol; they remain in the skin not more than 72 h and they passively sensitize the skin and mast cells of guinea pigs. It has been shown that IgE fix mast cells

and basophils [4, 5]. Fixation takes place through the Fc fragment of the IgE molecule. This is confirmed by the fact that the Prausnitz–Kuestner reaction can be inhibited by injection of an excess of myeloma IgE before or simultaneously with the injection of antibodies [8].

As regards the mechanism of the inhibitory action of peptides on allergic reactions of immediate type opinions differ. Some workers [2] consider that pentapeptides prevent fixation of IgE on mast cells and basophils by inhibiting the liberation of histamine from leukocytes and inhibiting the Prausnitz–Kuestner reaction, whereas others [6] regard the inhibitory effect of dipeptides as an antihistamine action. To resolve this problem of the mechanism of inhibition of PCA by dipeptides further investigations are needed.

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