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THE EFFECT OF A HISTAMINE-LIBERATOR ON THE CONTACT SENSITIZATION IN GUINEA-PIGS

By

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In allergic reactions of the anaphylactic type there is a liberation of histamine from the mast cells of the skin. The tissue response observed in these reactions has been explained as an effect of histamine on the permeability of the blood vessels.

In allergic reactions of the delayed type there is a locally increased amount of histamine which is believed to be carried there by the mononuclear cells (Inderbitzin, 1955). The accumulation of histamine in this area is probably a secondary phenomenon and without any significance in the development of this reaction (Fisher & Cooke, 1958). Except for a certain delay in healing, these authors could not find any difference concerning the sensitization to a contact allergen between control animals and guinea-pigs where histamine formation had been blocked through Germanin injections. Stern (1956) arrived, however, at entirely different results when sensitizing guinea-pigs to dinitrochlorbenzol. He gave them the histamine-liberator 48/80 during the sensitization period and in the majority of the animals the sensitization was inhibited.

These earlier studies which thus gave contradicting results concerning the importance of histamine in the delayed type of skin reactions made us interested in repeating Stern's experiments. We have used a more quantitative sensitization and

challenging technique than Stern. Furthermore we have worked with two different contact-allergens.

MATERIAL AND METHOD

Albino guinea-pigs of both sexes of about 300 grams each were used. The animals were fed on a pellet diet supplemented with cabbage.

Sensitization

In *series I* the animals were sensitized through application by a pipette of 0.002 cu.cm. of a 50 per cent solution of 1-chloro-2,4-dinitrobenzene (DNCB) in acetone.

The allergen solution was applied to an area of the skin measuring approximately 3 sq.mm. located behind the right scapula where the hair had been pulled out. After application of the allergen the area was covered by adhesive tape.

In this series 51 animals were used, 26 of which received the histamine-liberator 48/80¹. The remaining 25 served as controls and received DNCB only. The dose was the same as given by Stern, namely one mg. 48/80 per kg. of body weight divided into two doses daily. The treatment with 48/80 was started seven days before the allergen injection and continued for ten days. The histamine-liberator was given subcutaneously into the rear part of the left flank.

In *series II* the animals were sensitized through one intracutaneous injection of 0.1 ml. of 1 per cent solution of para-fenylendiamine (PPD) in propylenglycol. The allergen was injected into the skin over sacrum.

In this series 19 animals were used, nine of which received 48/80 in the same dose as the one mentioned above. Treatment with 48/80 was started one day before the allergen injection and continued for another six days. The ten remaining animals served as controls and received PPD only.

¹ The compound was generously put at our disposal by AB Leo, Hälsingborg, Sweden.

The local effect of 48/80 on animals already sensitized was also studied. The animals in series II earlier treated with 48/80 received three days after the challenging with PPD a subcutaneous injection of 48/80 corresponding to 0.5 mg. per kg. body weight. This injection was given into an area on the back not earlier tested. On this area a 5 per cent solution of PPD was applied about 15 minutes later. The results were read after 24 hours as described below.

Challenging

Challenging of the skin reactivity was carried out ten days after the sensitizing injection. The test solution was applied with a pipette on a circular area of about 4 sq.cm. on the back of the animals. The hair had been cut off by an electric shaver.

Series I was tested with 0.05 cu.cm. of 0.09 per cent, 0.05 per cent, and 0.03 per cent solutions of DNCB in acetone.

Series II was tested with 0.02 cu.cm. of 5 per cent and 1 per cent solutions of PPD in absolute alcohol.

The skin reactions were read 24 hours after application of the test solutions and recorded according to the degree of intensity with the figures of 0.5, 1, 2, and 3. The degree of sensitization in the different series was arrived at by computing the average of the total skin reactions recorded in the series.

The sensitization as well as the challenging technique used is essentially the same as that described by Frey & Wenk (1956).

RESULTS

As shown in table 1 the frequency of positive animals was in both series about as large among the controls as among those treated with the histamine-liberator. The average of the degree of sensitization was somewhat higher in the animals that received 48/80. This difference is, however, not statistically significant.

By repeated challenging of series II with a 5 per cent PPD solution on a skin area pretreated by a subcutaneous injection

of 48/80, no significant difference was found between animals treated locally with 48/80 and controls, either in the frequency of positive animals or in the degree of sensitivity. However, even here the average degree of sensitization was somewhat higher in animals pretreated with 48/80 but not statistically significant (Table 2).

TABLE 1

The Effect of 48/80 on Contact Sensitization of Guinea-pigs with 1-Chloro-2, 4-Dinitrobenzene (DNCB) and Paraphenyldiamine (PPD).

	Controls		Treated with 48/80	
	Number positive	Intensity of reaction (Mean)	Number positive	Intensity of reaction (Mean)
Sensitized to DNCB	24/25	1.92	25/26	2.17
Sensitized to PPD	7/10	1.30	7/9	1.56

TABLE 2

The Effect of Local 48/80 Injection on the Skin Response to Parafenyldiamine in Sensitized Guinea-pigs.

Controls		Treated with 48/80	
Number positive	Intensity of reaction (Mean)	Number positive	Intensity of reaction (Mean)
7/10	1.20	6/8	1.50

DISCUSSION

By injecting guinea-pigs with 48/80 there would, according to Stern, be a decrease of histamine in the skin. This would explain the inhibiting effect of 48/80 that he observed on contact-sensitization. As support for the significance of histamine in contact-eczema Stern also states that in areas of guinea-pig skin especially rich in histamine, allergic contact-eczema develops more intensively.

Our own results show that in guinea-pigs repeated injections of 48/80 can not influence the development of the allergic reaction of the delayed type either if this histamine-

liberator is administered during the sensitization period itself, or after the animals have been sensitized.

Recent studies in this field indicate that repeated injections of 48/80, at least in some species, had a paradoxical effect on the histamine liberation. Schayer *et al.* (1959) have thus found that in rats such treatment results in a marked increase of histidine decarboxylase activity of the skin. According to these authors treatment with 48/80 probably leads to the production of new, resistant mast cells which are particularly active in forming histamine.

When Schayer *et al.* checked their results in guinea-pigs they could, however, not find this increased histidine decarboxylase activity. They put this in connection with the fact that 48/80 does not seem to have any effect on the concentration of mast cells and histamine in the guinea-pig skin (Mota & Vugman, 1956).

According to the investigations last cited there seems to be marked difference between rats and guinea-pigs concerning histamine metabolism in the skin. The future may reveal how much this has to do with the so far unsolved phenomenon that guinea-pigs can be easily sensitized to contact-allergens but rats only with difficulty.

SUMMARY

The histamine-liberator 48/80 was given to guinea-pigs simultaneously with a contact allergen. No significant difference in sensitization between controls and animals treated with 48/80 could be found. Neither did local 48/80 injection influence the skin response to a contact allergen in sensitized animals.

REFERENCES

- Inderbitzin, T.*: The Effect of Acute and Delayed Cutaneous Allergic Reactions on the Amount of Histamine in the Skin. *Internat. Arch. Allergy*, 7, 140, 1955.
- Fisher, J. P. & Cooke, R. A.*: Experimental Toxic and Allergic Contact Dermatitis. *J. Allergy*, 29, 396, 1958.

- Frey, J. R. & Wenk, P.*: Experimentelle Untersuchungen zur Pathogenese des Kontaktekzems. *Dermatologica*, 112, 265, 1956.
- Mota, I. & Vugman, I.*: Action of Compound 48/80 on the Mast Cells and Histamine Content of Guinea-Pig Tissues. *Brit. J. Pharmacol.* 11, 304, 1956.
- Schayer, R. W., Rothschild, Z. & Bisany, P.*: Increase in Histidine Decarboxylase Activity of Rat Skin Following Treatment with Compound 48/80. *Am. J. Physiol.* 196, 295, 1959.
- Stern, P.*: Die Bedeutung des Histamins in der Entstehung des Ekzems. *Arch. Int. Pharmacodyn.* CV, No. 3-4, 1956.

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