

Original Articles

EXPERIMENTS ON HISTAMINE REFRACTORINESS

III. THE EFFECT OF HISTAMINE PRETREATMENT ON THE ESTABLISHMENT OF ACTIVE SENSITIZATION*†

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PRETREATMENT of serum-sensitized guinea pigs with histamine induces decreased anaphylactic response in these animals. This was shown by Farmer^{1, 2} using the Schultz-Dale technique and later by Karady³ in the intact animal. In Farmer's experiments histamine pretreatment was instituted at the height of sensitization. In Karady's work it was carried out before, during, and through the sensitization period.

It was concluded from these experiments that the lesser degree of anaphylactic reactivity is due to increased histamine tolerance and these experiments were interpreted as providing further indirect evidence of the correctness of the histamine theory of anaphylaxis. As an alternative explanation one could assume that the decreased anaphylactic response is due to interference with the immunologic process, i.e., that histamine pretreatment leads to a lesser degree of anaphylactic sensitization.

Passive sensitization experiments should further clarify these questions. By carrying out the anaphylactic experiment in passively sensitized "normal" guinea pigs, i.e., guinea pigs which had not been pretreated with histamine but which had been passively sensitized with the serum of (a) actively sensitized normal guinea pigs and (b) actively sensitized and histamine-pretreated guinea pigs, it would be possible to ascertain if histamine pretreatment had exerted an effect on the establishment of active sensitization.

EXPERIMENTAL

I. Control Experiments.—Male guinea pigs, weighing on an average from 180 to 250 grams, were actively sensitized by one intraperitoneal injection of 0.5 c.c. normal horse serum diluted 1:10. Twenty-one days later the animals were bled from the heart, the serum was pooled and thirty-four normal male guinea pigs, weighing on an average from 200 to 300 Gm., were each passively sensitized by an intraperitoneal injection of 5.0 c.c. of this serum. Twenty-four hours later these animals were given an intravenous injection of 0.4 c.c. normal horse serum. Eight animals, or 23.5 per cent, died in shock.

II. Histamine Phosphate Pretreatment Experiments.—Male guinea pigs, weighing on an average from 180 to 250 grams, were actively sensitized by one

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intraperitoneal injection of 0.5 c.c. normal horse serum diluted 1:10. Histamine pretreatment was instituted the next day, according to the schedule used by Karady. The animals received a total of thirteen intraperitoneal injections of histamine acid phosphate over a period of 19 to 20 days. The first seven injections of 5, 10, 20, 40, 60, 80, and 100 γ per 100 Gm. of body weight were given on successive days. The eighth to thirteenth injections, which were 100 γ per 100 Gm. of body weight each, were given at one to two day intervals. Two days after the last histamine injection, or twenty-one or twenty-two days after the sensitizing injection, the animals were bled from the heart and the serum was pooled. Each of thirty-seven normal guinea pigs, weighing on an average from 230 to 330 Gm., were passively sensitized by an intraperitoneal injection of 5.0 c.c. of this serum. Twenty-four hours later these animals were given an intravenous injection of 0.4 c.c. normal horse serum. Seven guinea pigs, or 18.9 per cent, died in shock.

III. Histamine Azoprotein Pretreatment Experiments.—Male guinea pigs, weighing on an average from 180 to 250 grams, were actively sensitized by one intraperitoneal injection of 0.5 c.c. normal horse serum diluted 1:10. Beginning the next day the animals were given thirteen intraperitoneal injections of histamine azoprotein at intervals of one to three days. In the first two groups of animals, undiluted histamine azoprotein was used. The guinea pigs did not tolerate the injections well and I later used 1:10 and 1:100 dilutions. Varying amounts of histamine azoprotein were given. In the first group of animals 0.47 c.c. per 100 Gm. of body weight, and in the second group 0.22 c.c. per 100 Gm. of body weight were used. The mortality rate in both of these groups was very high. I therefore reduced the total amount of histamine azoprotein used for pretreatment to 0.20 c.c. per 100 Gm. of body weight. This amount was given in a 1:100 dilution. Twenty-four hours after the last histamine azoprotein injection the animals were bled from the heart, their serum was pooled, and thirteen normal male guinea pigs, weighing from 220 to 320 grams, were passively sensitized by an intraperitoneal injection of 5.0 c.c. each of this serum. Twenty-four hours later these animals were given an intravenous injection of 0.4 c.c. normal horse serum. Three guinea pigs, or 23 per cent, died in shock.

TABLE I

CONTROL EXPERIMENTS			HISTAMINE PHOSPHATE PRETREATMENT			HISTAMINE AZOPROTEIN PRETREATMENT		
TOTAL ANIMALS SHOCKED	FATALITIES		TOTAL ANIMALS SHOCKED	FATALITIES		TOTAL ANIMALS SHOCKED	FATALITIES	
	NO.	%		NO.	%		NO.	%
34	8	23.5	37	7	18.9	13	3	23

SUMMARY AND CONCLUSION

Table I summarizes the results of all experiments. It shows that the percentage of fatalities was virtually the same in the three groups of animals which were passively sensitized by the serum (a) of sensitized "normal" guinea pigs, (b) of sensitized guinea pigs pretreated with histamine phosphate,

and (c) of sensitized guinea pigs pretreated with histamine azoprotein. This indicates that pretreatment with histamine phosphate or histamine azoprotein did not interfere with the establishment of active sensitization. One may, therefore, conclude that the lesser degree of anaphylactic reactivity which was observed by Farmer and Karady in sensitized and histamine-pretreated guinea pigs was due to increased histamine refractoriness.

REFERENCES

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3. Karady, E. S.: Histamine Tolerance and Anaphylactic Death in Sensitized Guinea-Pigs, *J. Immunol.* **41**: 1, 1941.