IMPORTANCE OF HISTAMINE IN THE ACTION OF CORTISONE ON VASCULAR PERMEABILITY

(UDC 612.135 : 612.014.462.1-06 : 615.361.45]-06 : 615.787)

E. M. Mikhailova

Department of Pathophysiology (Head—M. M. Pavlov),
1st Acad. I. P. Pavlov Leningrad Medical Institute
(Presented by P. S. Kupalov, Active Member, Academy of Medical Sciences, USSR
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 58, No. 7,
pp. 27-30, July, 1964
Original article submitted February 5, 1963

It has recently been shown that ACTH and cortisone reduce vascular permeability. The mechanism of this influence is still unclear. The majority of investigations have been devoted to studying the action of the adrenocortical hormones on capillary permeability and inflammatory exudation. It has been established that ACTH and cortisone inhibit the inflammatory reaction and also cuase attenuation of allergic reactions [1, 3, 6, 8, 10, 13-16].

In previous investigations we observed a change in the cellular composition of the exudate in experimental peritonitis of rats under the influence of ACTH, and retardation of the development of Arthus' phenomenon in sensitized rabbits on administration of ACTH. Establishment of the manifest influence of cortisone on capillary permeability in the presence of local pathological processes accompanied by liberation of histamine naturally forced us to assume that cortisone affects histamine, its liberation, and its breakdown.

Glin [9] did not note any direct antihistaminic action for cortisone. Gruenspan [10] indicates the participation of cortisone in the synthesis, accumulation, and release of histamine. Schou [15] established that liberation of histamine is important in the absorption of subcutaneously injected substances. Injection of substances which deplete the histamine supply led to retardation of absorption. Administration of cortisone reduced this effect in rabbits and, to a lesser extent, in rats. The author notes that the liberation of endogenous histamine from fat cells in the presence of traumas and other pathological processes is slight.

A more detailed study of the influence of cortisone on vascular permeability, which was increased by the action of histamine, was of interest. We studied the rate and extent of elimination of the colloidal dye trypan blue from the blood, comparing the "purification" under the action of histamine and of a combination of histamine and cortisone.

EXPERIMENTAL METHOD AND RESULTS

In our experimentation we used 137 white rats of mixed breeds. All the experimental animals were injected intravenously with a 1% trypan blue solution in a dose of 0.3 ml per 100 g of body weight.

In the experiments of series I (85 rats) we elucidated the influence of cortisone on the action of administered histamine, which increases the permeability of the vascular walls to colloidal dye. One group of rats (34) was injected intramuscularly with 25 ml of cortisone $1\frac{1}{2}$ h before the dye was administered; 17 of them were injected subcutaneously with 0.01 g of histamine 30 min before the dye was administered. Another group of rats (17) was given histamine only. The control group was composed of 34 rats, which received only an injection of the trypan blue solution. In this series of experiments blood was taken from the carotid arteries of all the animals 1 h after administration of the dye and the dye concentration in the plasma was determined colorimetrically in a FEK-M1 electrophotocolorimeter.

As may be seen from Table 1, the blood of the animals which received histamine contained considerably less dye than in the control. The dye content of the blood of the rats which received cortisone only was greater than

TABLE 1. Trypan Blue Concentration in Blood Plasma of Rats

Experimental conditions	Mean index	Difference	P
Control	$6.0 \cdot 10^{-3}$%±0.2	–	
Cortisone	$9.0 \cdot 10^{-3}$%±1.0	3.0	< 0.0013
Histamine	$3.5 \cdot 10^{-3}$%±0.3	2.5	< 0.0013
Histamine and Cortisone	$4.5 \cdot 10^{-3}$%±0.4	1.5	< 0.006

TABLE 2. Trypan Blue Concentration in Blood Plasma of Rats

Experimental conditions	Mean index	Difference	P
Control	$6.1 \cdot 10^{-3}$% ±0.4	2.3	< 0.001
Egg white	$3.8 \cdot 10^{-3}$% ±0.3		
Cortisone and egg white	$4.0 \cdot 10^{-3}$% ±0.2	2.1	< 0.001

that for the control animals. At the same time, the dye concentration in the blood of the animals which received both cortisone and histamine did not differ materially from that in the blood of the animals which were given histamine only (the difference was not statistically reliable).

The cortisone thus somewhat inhibited the escape of the dye from the blood. No significant difference was noted in the dye content of the blood of the white rats which received cortisone and histamine or histamine alone.

On the basis of our observations it may be assumed that cortisone does not influence the action of administered histamine on vascular permeability.

In experiments on rats, Halpern and Neveu [11] established that there is a difference in the fixation and elimination of exogenous and internally liberated histamine. Endogenous histamine accumulates in the fat cells and is fixed in other tissues; exogenous histamine disappears very rapidly from the blood and is fixed in the kidneys and, to a lesser extent, the stomach.

The difference in the fixation and elimination of administered and endogenously formed histamine enables us to assume that cortisone may influence only the effects of endogenous histamine. A. I. Yakovleva [7] has shown that the number of fat cells and their form are altered under the influence of cortisone.

In the experiments of series II we attempted to elucidate the influence of cortisone on the action of endogenously liberated histamine. Many substances can release histamine. Dextran, peptone, preparation 48/80, and egg white are used for this purpose in experimental investigations. The effectiveness of these substances differs in different species of animals. Selye [16] and other authors believe that egg white is the most effective liberator for rats. Ma Bao-Li [2] observed an increase in histamine concentration in the blood on administration of highly dilute (1:100) egg white to rats. We employed egg white as a histamine liberator for rats.

Our subjects were 52 white rats of mixed breeds, weighing 160-180 g. In order to liberate histamine the animals were injected intraperitoneally with egg white diluted to 1:2 in physiological solution; some of the animals were given egg white intravenously in a dilution of 1:10. Forty to fifty min after injection of the albumin a 1% trypan blue solution was injected intravenously in a dose of 0.3 ml per 100 g of body weight. We assume that this time was sufficient for absorption of the albumin and liberation and partial elimination of histamine. Vallecalle et al. [17] observed edema of the paws and muzzle in rats after intravenous injection of dextran; histamine disappeared from the skin within 4 h and its content returned to normal only after several days. We assumed that the albumin was gradually absorbed over 40-50 min after it was injected and that histamine was liberated under its action; it was impossible to obtain a complete disappearance of histamine. Thirteen animals were injected intramuscularly with 25 mg of cortisone $1\frac{1}{2}$ h before administration of the albumin. One h after intravenous injection of trypan blue blood was taken from the carotid arteries of all the experimental animals and subjected to colorimetry for determination of its dye content.

It may be seen from Table 2 that somewhat less dye was detected in the blood of the animals which received albumin in that of the control animals. This enables us to assume that administration of albumin caused liberation of histamine, which may also explain the intensive elimination of the dye from the blood of these animals.

In comparing the data obtained for the animals which were given albumin and those which were given albumin and cortisone, it may be noted that the cortisone did not influence the action of the albumin with respect to liberation of histamine (the differences was not statistically reliable). In both groups of animals the trypan blue content of the blood 1 h after the dye was injected intravenously was less than that for the control animals. The results of this series of experiments enable us to assume that cortisone does not effect the liberation of histamine by albumin. It is possible that the interaction of cortisone and histamine is far more complex.

In the experiments of series III we studied the influence of cortisone on the local action of histamine on the cutaneous vessels.

Our subjects were 15 white rats weighting 160-180 g. We injected 0.01 g of histamine in 0.2 ml of liquid and egg white diluted to 1:10 in the same volume of liquid beneath the skin of the abdominal wall at various points.

Some of the animals (10) were preliminarily given 12 mg of cortisone. All the experimental animals were injected intravenously with a 1% trypan blue solution in a dose of 0.3 ml per 100 g of body weight before the subcutaneous injections.

The extent to which the skin was stained at the sites of injection of egg white and distilled water was found to be the same in the animals which received cortisone and in the control animals. The most intensive staining was observed at the sites where histamine and egg white were injected.

LITERATURE CITED

1. I. I. Islamov, Trudy Dushanbinsk. med. inst., Vol. 21, No. 3, p. 141 (1956).
2. Ma Bao-Li, Pat. fiziol., No. 5, p. 14 (1959).
3. G. L. Mednik, Trudy Dushanbinsk. med. inst., Vol. 21, No. 3, p. 147 (1956).
4. K. N. Monakova, Ibid., p. 161.
5. I. A. Oivin, Farmakol i toksikol., No. 6, p. 50 (1959); Pat. fiziol., No. 3, p. 3 (1962); Trudy Dushanbinsk. med. inst., Vol. 21, No. 3, p. 5 (1956).
6. N. P. Smirnov, Byull. éksper. biol., No. 10, p. 28 (1955).
7. A. I. Yakovleva, Ibid., No. 9, p. 70.
8. E. P. Benditt, S. Schiller, H. Wong et al., Proc. Soc. exp. Biol. (N. Y.), Vol. 75, p. 782 (1950).
9. Glin, Dzh. Kh. Cortisone Therapy [Russian translation], Moscow (1960).
10. M. Grünspan, Stud. Cercet. Fiziol., Vol. 6, No. 2, p. 317 (1961).
11. B. N. Halpern and T. Neveu, J. Physiol. (Paris), Vol. 53, p. 358 (1961).
12. V. Menkin, Dynamics of Inflammation [Russian translation], Moscow (1948).
13. V. H. Moon and G. Tershakovec, Proc. Soc. exp. Biol. (N. Y.), Vol. 79, p. 63 (1952).
14. K. Mitsch, Klin. Wschr., Bed. 30, S. 228 (1952).
15. J. Schou, Acta pharmacol. (Kbh.), Vol. 15, p. 43 (1958).
16. H. Selye, Canad. med. Ass. J., Vol. 61, p. 553 (1949).
17. E. Vallecalle, S. A. Conraler Lague and T. Garkido de Armas, Acta cient. vener., Vol. 9, p. 56 (1958).

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
