

INFLUENCE OF HISTAMINE AND ANTIDIURETIC HORMONE
ON DIURESIS AND RENAL EXCRETION OF THE ENZYME
HYALURONIDASE

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M. S. Yaremenko and N. P. Kushch

Laboratory of the Physiology of Excretion (Supervisor—Candidate of Biological Sciences, B. E. Esipenko), A. A. Bogomolets Institute of Physiology (Director—Academician of the Academy of Sciences of the UkrSSR A. F. Makarchenko), Academy of Sciences of the UkrSSR, Kiev
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In the investigations of A. G. Ginetsinskii et al. [2-5, 7], and then in the studies of other authors [11-15], it was established that the effect of antidiuretic hormone (ADH) on the kidneys requires the participation of the enzyme hyaluronidase. It is known that in addition to ADH, there is a whole series of biologically active substances, such as aldosterone, adrenalin, acetylcholine, and histamine, which are also capable of inhibiting the diuretic function of the kidneys by intensifying the process of reabsorption of water in the kidney tubules. However, the mechanism of the action of these substances upon the kidney is unclear.

In view of this, the question arises of whether the enzyme hyaluronidase participates in the antidiuretic effect of these substances upon the kidney. Histamine is of special interest, since it is known that it manifests not only an antidiuretic action [1, 12], but also a pronounced ability to activate the enzyme hyaluronidase in vitro [8, 10]. According to the latest data of A. G. Ginetsinskii and V. F. Vasil'eva [5], all antihistamines are simultaneously antihyaluronidases and exert an action opposite to that of ADH upon the kidneys.

Consequently, there are literature data indicating that there is a definite relationship between histamine and the hyaluronidase-hyaluronic acid system.

The purpose of this investigation was to establish whether the enzyme hyaluronidase participates in the antidiuretic effect of histamine upon the kidney. For comparison, we also studied the reaction of the kidney to ADH at the same time.

EXPERIMENTAL METHOD

The investigations were conducted in chronic experiments on dogs with the ureters excised according to the method of I. P. Pavlov and with gastric fistulas. The response of the kidneys to histamine and ADH was studied at various initial levels of urination. In the first series of experiments, histamine and ADH (pituirgin P was used) were administered to the animal against a background of a relatively low level of diuresis (2-2.4 ml/min per m² of body surface), which was created by continuous intravenous infusion of a 0.6% sodium chloride solution at a rate of 2 ml/min; a total of 200 ml of the solution was introduced during the experiment. In the second series of experiments, the effects of these substances were studied under conditions of high diuresis (the rate of urination was 10-12 ml/m² · min). Such a level of urination was achieved by a single introduction of water into the stomach of the dog in an amount comprising 5% of the body weight, followed by intravenous infusion of a 0.6% sodium chloride solution at a rate of 10 ml/min.

The experimental procedure was the following. After stabilization of diuresis at the required level for 30 min, six portions of urine were collected at 5 min intervals, and then the animals received intravenous injections of hist-

TABLE 1. Magnitude of Diuresis (in ml in 20 min) and Hyaluronidase Activity of the Urine (in Arbitrary Viscosimetric Units) after Intravenous Injection of Histamine (5 μ g/kg) and Pituitrin (0.001 ME/kg) with a Low Initial Level of Urination

Index	Initial level	Histamine		Initial level	Pituitrin	
		first injection	second injection		first injection	second injection
Diuresis	44.0	22.6	36.0	45.5	16.0	26.0
Hyaluronidase activity	0-3	30.5	18.7	0-4	38.2	23.0

TABLE 2. Magnitude of Diuresis (in ml in 20 min) and Hyaluronidase Activity of the Urine (in Arbitrary Viscosimetric Units) after Intravenous Injection of Histamine (10 μ g/kg) and Pituitrin (0.001 ME/kg) against a Background of a High Level of Urination

Index	Initial level	Histamine		Initial level	Pituitrin	
		first injection	second injection		first injection	second injection
Diuresis	223	98	124	229	60	90
Hyaluronidase activity	0	29	17	0	23	23

amine or pituitrin. Then 40-60 min after the effect from the first injection of these substances had disappeared and diuresis was restored to the initial level, the animals were given repeated injections; moreover, pituitrin was administered after histamine, and vice versa. In the case of a low initial level of diuresis (experimental series I), histamine was administered in a dose of 5 μ g/kg of body weight, while in the case of high diuresis (experimental series II), the dose of histamine was doubled. In both series pituitrin was administered in a dose of 0.001 ME/kg. The hyaluronidase activity of the urine was determined by a viscosimetric method in Yu. V. Natchin's modification [9].

RESULTS

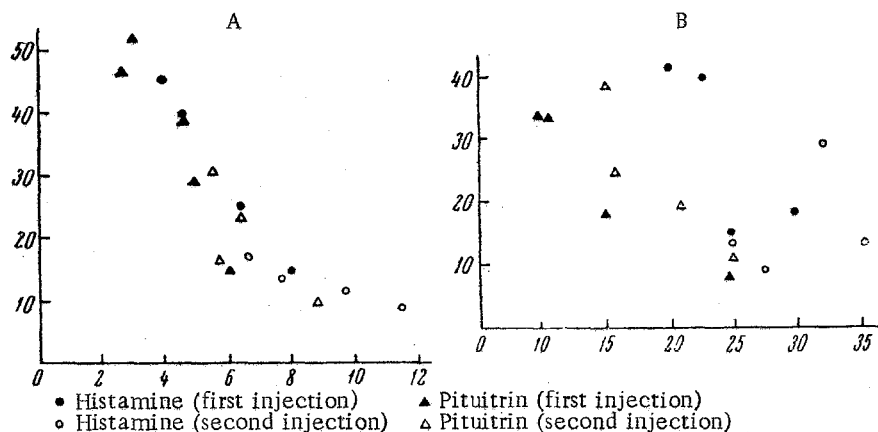
As can be seen from Tables 1 and 2, intravenous injection of small doses of histamine and pituitrin give rise to a regular decrease in diuresis among the dogs and a simultaneous appearance of hyaluronidase activity in the urine.

Consequently, the antidiuretic response of the kidneys to histamine, just like that to pituitrin, is accompanied by the appearance of the enzyme hyaluronidase in the urine.

According to the data of A. G. Ginetsinskii [6], the relationship between the activity of the urine and diuresis is a strict law. With increasing diuresis, the hyaluronidase activity of the urine decreases. It has been established that this dependence is due not to the effect of dilution, but to a sharp decrease in the entry of ADH into the blood under conditions of water diuresis.

It was of definite interest to establish the relationship between the extent of urination and the hyaluronidase activity of the urine after the reaction of the kidney to histamine and pituitrin. On the graph (see A, figure) is presented the relationship between these quantities after the injection of pituitrin and histamine against a background of low initial diuresis (see A, figure) and under conditions of intensive water diuresis (see B, figure). As can be seen from the data cited in the figure, under conditions of relatively low diuresis, the points expressing the relationship between the activity of the urine and diuresis are distributed uniformly. It is important that for the same level of diuresis, the hyaluronidase activity of the "histamine" urine is approximately the same as that of the "pituitrin" urine. Thus, in the case of a low initial level of diuresis, the hyaluronidase reactions of the kidneys to histamine and pituitrin are quite identical.

Somewhat different patterns were noted when the dogs were administered histamine and pituitrin against a background of intensive water diuresis. As can be seen from Table 2, after the injection of histamine and pituitrin, the urination is substantially reduced, but still remains at a level three to four times as high as in the preceding



Hyaluronidase activity of "histamine" and "pituitrin" urine in the presence of low (A) and high (B) water diuresis. Along X-axis — diuresis (in ml/m² in 5 min); along Y-axis — hyaluronidase activity (in arbitrary viscosity units).

series of experiments (see Tables 1 and 2). However, the urine acquires hyaluronidase activity approximately the same as in the experiments with a low initial level of urination. In such a comparison of the data, we immediately detect a lack of agreement between the magnitude of diuresis and the hyaluronidase activity of the urine.

The difference in the antidiuretic and hyaluronidase reactions of the liver to histamine and pituitrin in the case of high diuresis is especially distinct if we compare the relationship between the hyaluronidase activity of the urine and diuresis graphically. From the figure, B, it is evident that for equal diuresis, the "histamine" urine exhibits greater activity than the urine obtained after injection of pituitrin. As a result of this, all the points on the graph, expressing the ratio between the value of diuresis and the hyaluronidase activity for histamine are situated higher than the corresponding points for pituitrin. This difference is evidently due to the fact that the histamine excreted with the urine is capable of activating hyaluronidase, while ADH does not possess such ability.

If our hypothesis of the activating influence of histamine upon the urine hyaluronidase is correct, then we should have expected that the addition of histamine to the urine would increase the hyaluronidase activity of the urine. To clarify this question, we conducted a series of experiments in which we studied the hyaluronidase activity of the urine before and after the addition of histamine (10 µg/kg) or pituitrin (0.001 ME/kg) to it. It was found that the addition of histamine to the urine caused a substantial increase in the activity of the hyaluronidase contained in it, while pituitrin did not affect the activity of this enzyme.

In experiments with a low diuresis, the negligible activating effect of histamine is evidently due to the low histamine content in the urine, since in these experiments the animal received half the dose of this substance in comparison with that in the experiments with high diuresis.

The basic conclusion that may be drawn from this work is that the antidiuretic effect of histamine, just like that of ADH, is accompanied by the appearance of the enzyme hyaluronidase in the urine. Whether histamine acts directly upon the kidneys, stimulating the liberation of the enzyme hyaluronidase by the cellular elements of the nephron, or whether it only increases the release of ADH into the blood, which then exerts a direct influence upon the kidney, is unclear. The resolution of this question will require further investigations.

SUMMARY

Experiments on dogs with ureters exposed by Pavlov's method were used to study the influence of a single intravenous injection of histamine and antidiuretic hormone (pituitrin) on the water excreting function of the kidney and excretion of hyaluronidase enzyme with urine. It was established that injection of histamine as well as of antidiuretic hormone caused a reduction in diuresis with a simultaneous appearance of hyaluronidase enzyme in the urine; at the same time, as the enzyme concentration in the urine became greater the more considerable was the reduction of diuresis.

The results of the investigations give ground to suppose that the antidiuretic effect of histamine on the kidney is partly due to the presence of hyaluronidase enzyme.

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