Heparin and the Water Metabolism with Special Reference to the ADH

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It was Raynaud and his co-workers\(^2\) who in 1952 published at first their observations on the diuretic effect of heparin. The edema in a woman with congestive heart failure disappeared after the administration of heparin. Engelberg\(^1\) observed a similar effect in a patient with Kimmelstiel-Wilson syndrome. In the following years French and Belgian authors,\(^3\) reported on their observations. In their patients with nephrosis syndrome, heparin caused a considerable diuresis. Then, many authors have examined the mechanism of the diuretic effect of heparin; that is, its point of attack.

Heparin causes diuresis in the cases of edemas of different etiology.\(^2\) Its character differs from that of the other diuretics, such as mercurials, chlorothiazide and carbonic anhydrase inhibitors, in that the effect is of the delayed type: it appears about 36-48 hours later, and lasts about 48 hours after the termination of medication. According to the data in the literature the quantity of heparin and the way of its administration varied considerably. The majority of the authors used dosages of 300 mg heparin for 3-4 days.

As a manifestation of the diuretic effect, besides a strikingly large sodium chlorine excretion, a moderate urine excretion and slight potassium retention may be observed. All these occur in the distal renal tubuli. This excretion form is similar to that, which may be found in patients suffering from Addison’s disease, or to that brought about on administration of Amphenone or Spirolactone.

Based on these observations Majoor and co-workers\(^5\) presumed that the effect of heparin is produced through the intermediation of the adrenal cortex-by inhibiting aldosterone secretion.

In case of secondary aldosteronism several authors\(^1\),\(^2\) observed decrease of aldosterone excretion following the heparin administration. Majoor,\(^2\) however, mentioned 12 patients: 2 cases of Addison’s disease, 6 cases of congestive heart failure, 3 cases of nephrosis syndrome and 1 case of mephritis chr. in which...
heparin decreased considerably the sodium excretion and did not cause diuresis.

It may be assumed that in the occurrence of heparin-diuresis, besides its effect produced on aldosterone, other factors play a role as well. Basing on our observations with the antidiuretic hormone, we thought that the effect of heparin could be possibly brought about also through this axis. The purpose of our investigation was to determine whether a correlation exists between the action of heparin and ADH system.

METHODS

In the present experiments we used the method elaborated and described by one of us (J.H.). The method helps us observe the ADH katabolism in the organism.

The effect of a known quantity of ADH may be judged, only when the endogenous ADH is eliminated, for which the water-loading is the most appropriate; 150 ml water was brought every 15 minutes by means of a duodenal tube, thus steady hydration and high minute-diuresis being ensured. This stops the production of endogenous ADH, and the circulating ADH disappears completely from the organism in about 15–20 minutes. As soon as the minute-diuresis attained a due value of 10–12 ml/min., crystalline pitressin in 0.5–1.0 mU/kg body weight was injected intravenously, as a result of which an abrupt fall in the minute-diuresis could be observed.

In the course of our examinations we established at first a pitressin curve, and then 25,000U heparin was injected intravenously. About 5 or 15 minutes later another dose of pitressin was given in order to determine whether the heparin influenced the course of the curve, the curve thus obtained being compared with the control curve. The response to heparin was considered as positive, when...
after heparin, pitressin of an identical quantity induced a smaller antidiuresis than the control. In some cases the antidiuretic effect of pitressin was completely missing after heparin (Fig. 1).

The tests were carried out on two patients every time, the diagnosis of whom varied, but who were normal from the viewpoint of water metabolism. Two of our patients suffering from diabetes insipidus were advisedly included among the subjects.

RESULTS

Examinations were made in 18 cases. In 4 of these the heparin perfectly blocked the effect of pitressin given subsequently, and no antidiuretic effect occurred at all. In further 6 cases it reduced the effect of pitressin. In the remaining 8 cases it had no essential influence upon it.

According to our results, in more than 50% of the cases the antidiuretic effect of pitressin was inhibited by heparin. We have yet no explanation as to why the pitressin curve was influenced by heparin or not. Neither dosage, the time passed between the two injections, nor the nature of the illness are of any importance. The hormonal background however may play a part here. This is a problem for further investigation.

DISCUSSION

Numerous observations have hitherto been reported on the effect of heparin on the water metabolism. As regards its mechanism various hypotheses have been put forward.

According to a considerable part of the authors, aldosterone would play a role in the occurrence of heparin-diuresis. Four systems may be supposed at present to be involved in the regulation of aldosteron secretion; i.e.

1. A central regulator in the diencephalo-hypothalamic region.

This regulator is supposed to be localized in the posterior part of the diencephalon, in the region of the pineal body, in the grey matter surrounding the central aquaeduct. It is probable that in a humoral way—by the help of the assumed, but not verified glomerulotropin— the regulating function of this central factor is working.

2. Volume receptors.

The localisation of two volumeters is known at present; one may be found at the remification of the A. carotis communis and the A. thyreoidea inferior. In the case of the decrease in the intravasal pressure or hypovolemia, aldosterone hypersecretion may be observed.

The other having an inhibitor effect is found in the right atrial wall. A
dilatation of the right atrium may result in a decrease of the aldosterone secretion.

3. **Angiotensin-renin.**

The aldosterone production of the zona glomerulosa of the suprarenal gland is supposed to be regulated as "trop" hormone by the renin produced by the juxtaglomerular renal cells. In patients suffering from malignant hypertonia aldosterone hypersecretion was found in every cases.23)

4. **Sodium and potassium ions.**

The Na and K ions have direct influence upon the aldosterone level, their effect is produced through the intravasal space, by the change in the hemoco- ncentration, and in the vascular volume.26,2) Some authors presume, however, that the K ion has a direct influence on the volume receptors.23) Na administration decreases the mineralocorticoid secretion, and its withdrawal increases the secretion. K has an opposite effect.

It seems that the volumeters would not take part in the production of the aldosterone-decreasing effect of heparin. Majoor and co-workers24) never observed hypercirculation in their patients. On the other hand, K-retention following the heparin-diuresis is in contrast to the mechanism of hypercirculation, which rather entails a decreased K-level.10)

Those who explain the heparin diuresis by the participation of aldosterone assume that the effect of heparin may come about by decreasing aldosterone output like that of Amphenone, or by blocking the steroid effect through competitive antagonism like that of Spirolactone, or by increasing the katabolism, and elimination of aldosterone (Cejka11)).

According to Mario Ravera’s opinion,30) the heparin-diuresis would be due to the increase in the plasma-volume, as well as to the increased permeability of the vasal membrane.

According to others, heparin would have one more effect, i.e., a decreasing effect on the ACTH secretion16,17,15,6) in the way of the pituitary-adrenal gland axis.

As to the effect of heparin on the ADH and its mechanism, three possibilities may be taken into consideration:

1. Heparin may influence the ADH production. This presumption may be from the first excluded, for the reason that in our experiments heparin influenced immediately the effect of pitressin administered following it. This mechanism would be assumed only if the diuresis appeared 36–48 hours later.

2. Heparin may increase the ADH katabolism.

3. Heparin may competitively inhibit the ADH effect. This possibility seems to be the most probable explanation for the phenomenon we observed. The large dosage of heparin and also the temporal course of the effect support
this, though neither of these excludes the second possibility.

Our present concept on heparin-diuresis, and its mechanism is shown diagrammatically in Fig. 2.

Our explanations for this phenomenon are only hypothetical, and no convincing arguments support any of the mooted possibilities. Elucidation of this problem must await further investigation.

In any case it seems to be of importance, that the effect of heparin on the water-metabolism is, at least partly, brought about by the ADH system, as demonstrated in the present experiments.

**SUMMARY**

The authors demonstrated in the experiments on human subjects the correlation between the diuretic effect of heparin and the ADH-system. In more than half of their cases heparin inhibited the antidiuretic effect of pitressin. From this finding, the authors emphasized that the effect of heparin on the water-metabolism is at least partly brought about by the ADH-system.

**References**

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