RES MEDICA
Journal of the Royal Medical Society

Natriuretic Hormone

Heather A. Davis

Abstract

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(b) the activity of the renin-angiotensin-aldosterone system (Factor 2).
coupled with the effect of changes in intrarenal haemodynamics and physical factors, such as hydrostatic pressure surrounding renal tubules, and plasma protein osmotic pressure in peritubular capillaries.

Since that time, however, evidence has gradually been accumulated to suggest that these are not the only factors which are relevant in this context, and the existence of a humoral inhibitor of renal sodium reabsorption has therefore been postulated. This 'third factor' has been given the name of natriuretic hormone, and indications of its presence have been found in two principal situations. These are
(a) 'Sodium escape' during chronic mineralocorticoid administration
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    (ii) blood

ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)
Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Autumn 1973: 5-9
doi:10.2218/resmedica.v0i0.904

number of days in the lunar month (which is used in the Moslem calendar) and the number of letters in the Arabic alphabet. Nonetheless, the evident erudition of Moselm doctors compared to their western counterparts was so great that the more progressive of Christian physicians appreciated what was translated from their writings. Chaucer's **Doctor of Physick** has no less than six Moslems in his list of authorities:

"Well know he the old Esculapius,
And Dioscorides, and else Rufus;
Old Hippocras, Hali, and Gallien;
Serapion, Rasis, and Avicen;
Avarrois, Damascene and Constantin;
Bernard, and Gatisden, and Gilbertin".

Little wonder that Christian rulers who were in close communication with neighbouring Islamic states, as in partitioned Spain and in the Crusader-ruled Holy Land, used to send to the Moslems when they wanted a good physician!

I have attempted to give a brief outline of the debt our current medical practice owes to the great doctors of classical Islam, and in conclusion I cannot do better than quote from Meyerhof's authoritative work "The Legacy of Islam" —

"Looking back we may say that Islamic medicine and science reflected the light of the Hellenic sun when its day had fled, and that they shone like a moon, illuminating the darkest night of the European Middle Ages: that some bright stars lent their own light, and that moon and stars alike faded at the dawn of a new day — the Renaissance. Since they had their share in the direction and introduction of that great movement, it may reasonably be claimed that they are with us yet".

NOTE:

For those who wish to follow up this subject the writings of Edward Browne are recommended, who qualified in medicine, turned to Middle Eastern studies and went on to become Professor of Arabic at Cambridge. His scholarly work "Arabian Medicine" (C.U.P. 1921) is available from the Central Medical Library. The quotations in this article come from various sources and are translated either by Browne or by A. J. Arberry, the present Professor of Arabic to Cambridge University.

NATRIURETIC HORMONE

HEATHER A. DAVIS

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'Sodium escape' during chronic mineralocorticoid administration

When the extracellular fluid volume was expanded in healthy humans or dogs by chronic mineralocorticoid administration, an initial diminution of sodium excretion resulted, followed within a few days by a rise to control levels (2, 37). This 'sodium escape phenomenon' was attributed as early as 1957 to the existence of a circulating natriuretic hormone (37).

The presence of such a hormone was for some time disputed as many potential natriuretic factors have been identified during 'sodium escape' from chronic mineralocorticoid treatment. Other natrieuretic factors include deceased plasma renin concentrations, increased glomerular filtration rate and increased renal plasma flow. Sodium escape has, however, been shown to occur in the absence of each of these variables, thus indicating that none of them is critical to the escape mechanism (see 8).

Recently, additional evidence for the existence of a circulating natriuretic hormone has been provided by Buckalew and Lancaster in 1972 (8). They demonstrated the presence of a substance with natriuretic activity in ultrafiltrates of jugular venous plasma when 'sodium escape' occurred in dogs undergoing chronic administration of deoxycorticosterone acetate (DOCA).

Volume expansion with isotonic saline

There is much evidence to suggest that when the blood volume of an animal is expanded with isotonic saline, the rise in urinary sodium excretion which

occurs is due, in part, to a change in the concentration of a circulating hormone other than aldosterone.

The release of such a circulating natriuretic hormone was postulated by de Wardener et al, in 1961 (43). They demonstrated that in dogs receiving high concentrations of vasopressin and mineralocorticoid hormones, an intravenous infusion of isotonic saline produced a rise in urinary sodium excretion even when the glomerular filtration rate was deliberately lowered by inflating a balloon in the thoracic aorta. A natriuresis also occurred in denervated and isolated kidneys perfused with blood from volume expanded animals. The tubular reabsorption of sodium must therefore have decreased, and this decrease must have been caused by some mechanism other than a fall in the concentration of aldosterone. Similar experiments and cross-perfusion (19) experiments involving volume expansion with isotonic saline have confirmed these results (see 42).

An interesting experiment was devised by Richet and Hornych (32). They saline-loaded rats, and demonstrated that sodium reabsorption was inhibited both in the renal tubules and in a piece of the **in vivo** perfused jejunum in each rat. Aldo sterone pretreatment of the rats had no influence on this phenomenon. Since the two epithelial structures, which have common histological and immunological characteristics, were far apart, a natriuretic mechanism extrinsic to the kidney was postulated. They suggested that the natriuresis could have been mediated by a circulating hormone.

Volume expansion with blood

More precise evidence for the existence of a natriuretic hormone has been obtained from experiments in which the blood volume of animals was expanded with blood that was already in equilibrium with their own blood. Thus, haemodilution which is itself a natriuretic factor was excluded. A natriuresis was obtained using this method of volume expansion not only in whole animals but also in isolated kidneys perfused with blood from volume expanded animals. The volume expanded animals were treated with maximal doses of vasopressin and mineralocorticoid hormone and a natriuresis could be obtained even when the glomerular filtration rate was lowered (3, 20, 26, 39).

An elaborate experiment was performed by Tobian et al. (39) in which an isolated rat kidney was perfused with blood at a constant pressure (Fig.1). The kidney's only connexion with the rat which supplied it with blood was the blood itself. When a quantity of a mixture of two parts blood and one part Ringer's solution was placed into the venous reservoir without expanding the blood volume of the rat, there was no increase in sodium excretion by the isolated kidney (Fig. 1). When the same quantity of the mixture was infused intravenously into the rat and the blood volume expanded, there was in most instances a large rise in sodium excretion from the isolated kidney. This natriuresis was associated with a rise in renal blood flow and glomerular filtration rate. Since the rise in sodium excretion could not be attributed to haemodilution, renal nerve stimulation or a rise in arterial blood pressure, it was concluded that its cause must be a change in the concentration of a circulating substance which simultaneously increased renal blood flow by producing renal vasodilatation.

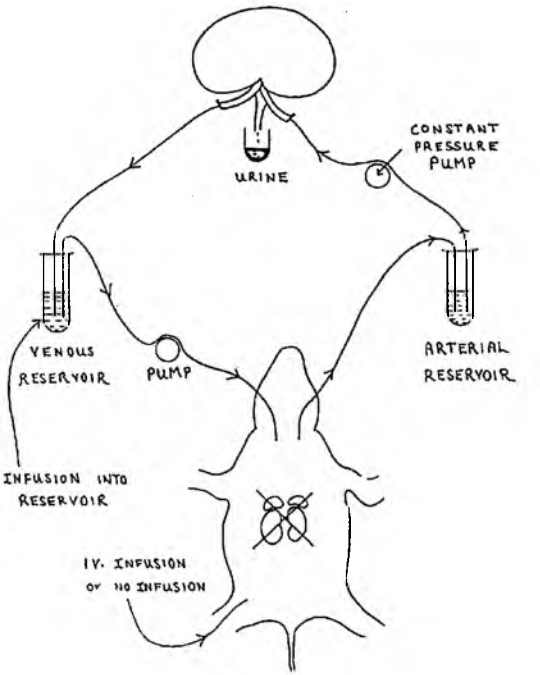

Fig. 1 Method used for determining the effect on urinary sodium excretion in an isolated rat kidney, of either diluting the blood or expanding the blood volume of the donor rat. The kidneys and adrenals were removed in the donor rat. (Tobian, Coffee and McCrea, 1967).

Further evidence for the existence of a circulating natriuretic hormone

This has been obtained from the detection of natriuretic activity in samples of plasma and urine. These sampes were collected from volume expanded man and animals, and humans with various clinical conditions. Natriuretic activity has been detected in the following —

(1) Plasma from saline-loaded dogs, rats, cats, sheep and cows (7, 9, 12, 31, 35) and plasma from dogs whose blood volume was expanded with blood (11, 30).
(2) Plasma and urine from intravenously saline-loaded normal man and man on a high salt diet (10, 35, 36, 41). Also urine from orally water loaded humans (22).
(3) Plasma and urine collected before and after saline loading of patients with primary aldosteronism (35, see 36).
(4) Plasma and urine from saline loaded patients with essential hypertension (35).
(5) Serum from uraemic patients (6, 7).
(6) Plasma from dogs during nephron reduction (7).
(7) Plasma from dogs (on a constant sodium intake) during 'sodium escape' as a result of chronic mineralocorticoid treatment (8).

Natriuertic activity has not however been detected in plasma and urine samples from humans on a low salt diet (35) or in urine collected from water loaded patients with congestive heart failure (22).

Assay preparations for the detection of natriuretic activity

Many in vivo and in vitro assay preparations have been developed for the detection of natriuretic activity in samples of plasma or urine. These are summarized below.

In vivo preparations

In most cases (6, 22, 35, 36, 41) the plasma and urine samples were concentrated and fractionated (using dialysis and ultrafiltration). Natriuretic activity was then detected in the samples by injecting or infusing them into assay rats and observing changes in urine flow and in sodium and potassium excretion from the bladder or ureters. The assay rats used in the different laboratories were under varying conditions of salt and water intake, and the samples were injected intravenously, intra-aortically, subcutaneously or directly into a renal artery.

Natriuretic activity has also been detected in unconcentrated plasma or dialysed plasma samples when they were injected directly into a renal tubule of an assay rat with hereditary diabetes insipidus. The rate at which the proximal tubular reabsorption of sodium was inhibited by the samples was determined by micropuncture (shrinking-drop technique) and by clearance techniques (31).

In vitro preparations

The transport of sodium, potassium and p-aminohippuric acid (PAH) has been studied in renal tubuls fragments which have been incubated in vitro both in untreated plasma (11) and in concentrated and fractionated urine (10) taken from man and animals before and after blood volume expansion. When incubated in plasma or urine obtained after volume expansion, tubule fragments were less able to maintain a constant gradient of sodium and potassium, or to accumulate PAH than when incubated in control plasma.

Blood from blood volume expanded dogs inhibited the transepithelial transport of sodium by the isolated frog skin (30). Similarly, this preparation was used to detect natriuretic activity in concentrated and fractionated samples of uraemic serum (6).

Concentrated and fractionated plasma samples from saline loaded dogs, or dogs in which 'sodium escape' from chronic mineralocorticoid administration had occurred, inhibited toad bladder sodium transport (9).

Mode of action of natriuretic hormone

When natriuretic activity was detected in samples of plasma and urine using in vivo assay preparations, the natriuresis was accompanied by an increased renal blood flow, a factor which itself produces a natriuresis. From these experiments, it was, therefore, impossible to determine whether the postulated natriuretic hormone acted by a direct action on renal tubular sodium transport. The subsequent use of in vitro assay preparations for the detection of natriuretic hormone showed, however, that the hormone directly inhibited the cellular mechanisms for active sodium transport.

Thus, it is probable that natriuretic hormone acts in vivo both by directly inhibiting tubular sodium transport and by producing renal vasodilatation.

Site of action of natriuretic hormone

Micropuncture techniques have revealed that the fall in sodium reabsorption with volume expansion takes place in the proximal tubules (14, 31). Proximal tubular sodium reabsorption is also inhibited when the sodium escape' phenomenon develops in more prolonged experiments in which the extra cellular fluid volume has been expanded by the administration of mineralocorticoids (44).

It has been reported that the distal tubule plays no regulatory rôle in the control of sodium excretion (5, 42). However, once proximal tubular sodium reabsorption has been maximally depressed during the administration of a saline load, the rate of sodium excretion can still be increased (13). Thus, the inhibition of sodium reabsorption in the distal segments of the nephron is also important in regulating sodium excretion during saline loading, and natriuretic hormone may act in these segments (13, 34, 35).

Source of natriuretic hormone

Many ablational experiments have been performed in an attempt to locate the source of the proposed natriuretic hormone. Many of these experiments were misleading as saline administration to animals produces a fall in plasma protein osmotic pressure and usually a rise in arterial blood pressure. Both of these changes evoke a natriuresis even in an isolated kidney perfused by a heart lung preparation. Thus, it is not surprising that the administration of saline to a decapitated dog with the adrenals, liver spleen removed, still produced a natriuresis (25).

Ablational experiments should, therefore, be performed using animals expanded with whole blood or blood with which their own blood is in equilibrium. Such an experiment, which was described earlier in this article, has been performed by Tobian et al., (39: see Fig 1). They suggested it was unlikely that natriuretic hormone was released from the adrenals or kidneys. Other workers have variously reported that natriuretic hormone could (19) and could not (33) be derived from the kidney. The liver (29, 38) and the brain (1, 12, 27, 37) have also been suggested as the source of the hormone. The origin of natriuretic hormone still remains uncertain.

Nature of natriuretic hormone

As a result of various attempts to detect natriuretic activity in plasma and urine samples, various reports as to the nature and properties of natriuretic hormone have resulted.

From studies using dialysis and gel filtration, the hormone has been reported to be non-dialysable and to have a molecular weight between 5,000 and 70,000 (35, 36). Other workers reported that the hormone was dialysable and had a molecular weight of less than 1,000 (6, 10, 12, 31). These conflicting results could readily be obtained if natriuretic hormone was a small molecule which was bound to a larger molecule (e.g. a plasma protein). In addition, natriuretic hormone has been variously reported to be a protein (35, 36), a polypeptide (12), to be resistant to boiling (6, 12, 35, 36) and to be stable only in the cold (31).

The natriuretic activity detected in some extracts displayed a delay in onset of up to one hour after injection and the effect lasted for up to three hours (35, 36). Again, these properties could suggest that natriuretic hormone was a small molecule which was slowly released from binding to a larger molecule. Other workers (31) however, found that their natriuretic material was rapid in onset (seconds),

with a short duration of action (less than thirty minutes). The hormone, which was effective on intravenous, intra-arterial or direct intratubular injection, has been reported to act primarily on sodium excretion and rarely to increase urine flow (31, 35, 36) but another report suggested that the hormone was more diuretic than natriuretic (12). The hormone produced an increase in renal blood flow 35, 36) but no change in potassium excretion or glomerular filtration rate. Natriuretic activity has been detected in both arterial and venous blood (31, 35, 36) but some workers were only able to detect the hormone in plasma samples which were concenrated before assay (6, 9, 10, 22, 31, 35, 36) whereas others detected it in blood or unconcentrated plasma (11, 12, 30, 31).

Some of the conflicting properties attributed to natriuretic hormone may result from the presence of contaminants in the plasma and urine extracts. Such contaminants could have been introduced during the concentration and fractionation procedures. In addition, bacterial endotoxins in urine samples have been shown to produce a potent natriuresis in assay animals (see Discussion after 36).

Natriuretic hormone and prostaglandins

It has been suggested that a prostaglandin could be a circulating (28) or intrarenal natriuretic hormone (23). Prostaglandins are a group of naturally occuring 20-carbon fatty acids which contain a cyclopentane ring and are derivatives of prostanoic

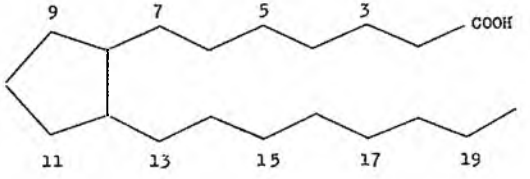

Fig. 2

acid (Fig. 2). Five series of naturally occurring prostaglandins have so far been described; namely the A, B, C, E and F series, all of which exhibit structural differences in the ring (Fig.3). The prostaglandins possess a wide variety of pharmacological actions (18).

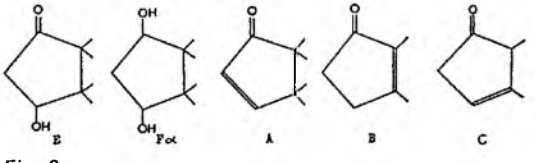

Fig. 3

Prostaglandins of the A and E series have been shown to produce a natriuresis and diuresis in dogs and rabbits when infused in very low concentrations either intra-aortically or directly into a renal artery (17, 28, 40, Davis, unpublished). Prostaglandin A1 produces a natriuresis when infused intra-aoretically in concentrations as low as 0.001 and 0.6 nanograms per millilitre of arterial blood in dogs and rabbits, respectively. Since prostaglandins of the A series (unlike the E series) are not metabolised by the lungs, they also produce a natriuresis when infused intravenously in similar concentrations, and they could be capable of acting as circulating natriuretic hormones (28).

It has also been proposed that prostaglandins of the A and E series could be intrarenal natriuretic hormones, as prostaglandins A2, E2 and F2α have been identified in the renal medulla of the rabbit, dog and rat (see 23). Lee (23) has suggested that when the extracellular fluid volume is increased, prostaglandins A2 and E2 could be released from the renal medulla to circulate intrarenally (possibly via the vasa rectae or lymph) to the renal cortex where they could stimulate a natriuresis. This theory is supported by the observations that the enzymes responsible for the synthesis of prostaglandins exist in the renal medulla, whereas the enzymes responsible for their degradation have been detected in high concentrations in the renal cortex and not the medulla (see 23. However, it is also possible that during volume expansion, prostaglandin A2 could be released from the renal medulla into the renal venous blood, circulate and then produce a natriuresis by an action in the renal cortex.

The natriuresis produced by prostaglandins and by natriuretic hormone is accompanied by vasodilatation in the renal cortex and an increase in renal blood flow. There is a redistribution of intrarenal blood flow from the medulla to the cortex. Glomerular filtration rate remains unchanged or increases slightly (see 23). It is not known whether prostaglandins stimulate a natriuresis in vivo solely by producing vasodilatation in the renal cortex, or whether they also exert a direct action on renal tubular sodium transport (16).

Since natriuretic hormone has been detected in samples of peripheral venous plasma, either a prostaglandin of the A series could have been detected or there is another circulating natriuretic hormone which either acts directly in the kidney to produce a natriuresis or stimulates the intrarenal release of prostaglandins of the A and E series.

Natriuretic hormone has also been detected in urine samples. Recently, prostaglandins E1, E2 and F2α have been identified in female human urine but no search was made for prostaglandins of the A series (15). Natriuretic activity in urine samples could, therefore, be attributable to the presence of prostaglandins of the E and possibly the A series.

Since the circulating concentration of prostaglandin A1 or A2 required to produce a natriuresis is very low and these prostaglandins are unstable in blood, no evidence for the release and circulation of these prostaglandins, during blood volume expansion, has yet been obtained (Davis, unpublished).

Clinical implications of natriuretic hormone

Natriuretic hormone has been associated with several clinical conditions, namely uraemia, aldosteronism, and congestive heart failure.

Uraemia

Since a natriuretic humoral substance was detected in the serum of uraemic patients, it was suggested by Bricker et al., (6, 7) that this hormone could serve in a homoeostatic rôle to increase the rate of sodium excretion per nephron as the number of nephrons diminished in advancing renal disease. Using experimental animals with nephron reduction, it has previously been shown

that the progressive natriuresis per nephron cannot be explained by a decrease in mineralocorticoid hormone activity, a change in glomerular filtration rate per nephron or by such physical factors as a change in cardiac output, mean arterial blood pressure, peripheral resistance or filtration fraction (see 6). It was also suggested (6) that in advanced renal disease, very high levels of natriuretic hormone could lead to the inhibition of sodium transport in extrarenal organs and contribute to the symptoms of the uraemic state.

Aldosteronism

Natriuretic activity was detected in extracts of urine and plasma samples collected, before saline loading, from patients with primary aldosteronism, but no such activity was detected in similar extracts from normal healthy humans (see 36). In addition, higher concentrations of natriuretic activity were detected in plasma and urine samples collected from saline loaded patients with primary aldosteronism than from normal humans (35, see 36). It is possible that in patients with primary aldosteronism, the enhanced basal and stimulated levels of circulating natriuretic hormone were released in order to offset excessive renal sodium retention produced by increased concentrations of aldosterone. This possibility is supported by the demonstration of a circulating natriuretic hormone in venous plasma taken from dogs during 'sodium escape' from chronic mineralocorticoid treatment (8).

Congestive heart failure

Krück (22) demonstrated that extracts of urine from orally water loaded humans possessed natriuretic activity, whereas similar extracts from water loaded patients with congestive heart failure possessed no such activity. He therefore suggested that an insufficiency or lack of natriuretic hormone in patients with congestive heart failure, could be an explanation for the increased renal tubular sodium reabsorption and development of oedema in cardiac disease.

Summary

A considerable amount of evidence has now been accumulated to support the existence of a circulating natriuretic hormone. Natriuretic activity has been demonstrated in plasma and urine samples collected during volume expansion with isotonic saline or blood, the administration of a high salt diet, 'sodium escape' during chronic mineralocorticoid administration and in certain clinical conditions. Under these conditions natriuretic hormone is released in detectable concentrations, but lower amounts of the hormone may be released continually, to participate in the regulation of sodium excretion. The chemical nature of the hormone still remains unknown, but a prostaglandin of the A series could be intrarenal natriuretic hormones.

Editor's note — A list of references provided by Dr. Davis is available from the Society's office.

ITEM OF MEDICAL INTEREST

The next day, as Candide was walking out, he met a beggar all covered in sores, his eyes were sunk in his head, the end of his nose eaten off, his mouth drawn to one side, his teeth as black as a coal, snuffling and coughing most violently, and every time he attempted to spit, out dropt a tooth.

(This was none other than Candide's old tutor, who described how he came to this state in these words)

"O my dear Candide, you must remember Pacquette, that pretty wench, who waited on our noble baroness; in her arms I tasted the pleasures of paradise, which produced these hell-torments with which you see me devoured. She was infected with the disease, and perhaps is since dead of it; she received this present from a learned cordelier, he was indebted for it to an old countess, who had it of a captain of horse, who had it of a marchioness, who had it of a page, the page had it of a Jesuit who, during his noviate had it from one of the fellow-adventurers of Christopher Columbus. For my part I shall give it to no-body for I am a dying man."

From Voltaire's "Candide", published in 1759.

THERAPEUTICS PROBLEM

A man attending an anti-coagulant clinic as an out-patient occasionally has unacceptably short prothrombin times. He claims to have been taking his tablets with religious regularity. He is rather surprised when the Doctor asks him what type of cooking oil his wife uses. Is this a relevant question? Answer on page 14.