

Regulation of Sodium Excretion: intra- and extrarenal mechanisms

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The control of salt and water balance is of much greater importance to the clinician than it is to the physiologist. The reasons for this are two-fold. In the first place, disease in man frequently leads to conditions of salt and water retention and were it not for the availability of efficient sodium diuretic (natriuretic) agents the clinician would be still more worried by the problems of oedema and heart failure. In the second place, the treatment of patients with water and electrolyte deficiency, e.g. in diabetic ketosis, severe diarrhoea or after surgical operations, is nearly always designed on the basis that the kidneys cope very well with an excess of salt. It is easier to treat the patient by giving an overload of salt and water, not only because the adjustment by the kidney is usually very good but also because intravenous fluids are a useful means of administering other substances to patients who are unable to take them by mouth or are likely to vomit.

There is a vast clinical literature on the subject of salt and water balance and many of the physiological studies have been prompted by clinical necessity. However, it is only in the last ten years that we have approached any real understanding of the subject. Even now we cannot pretend that we know all the answers. However, the more recent studies have thrown a completely different light on the means by which renal handling of sodium is regulated, and an appreciation of the mechanisms involved is obviously of physiological importance and is sometimes clinically essential.

In the 1940s it was recognised that changes in glomerular filtration rate could influence the rate of sodium excretion (Selkurt *et al.*, 1949). At the same time a different group of workers had established that the so-called amorphous fraction of adrenal extracts contained a substance that was life-saving in adrenalectomised animals. The implication that this effect was mediated by a change in sodium balance was made use of by Loeb (1933) when he maintained patients with Addison's disease by the administration of additional salt.

It was not until 1952 that Simpson and Tait, working at the Middlesex Hospital in London, isolated a new adrenal steroid which was later called

aldosterone and shown to be the most potent natural sodium-retaining steroid. It then appeared that the main facts about sodium control were established. The high excretion of aldosterone in patients with cirrhosis and ascites (Wolff *et al.*, 1958) and with the nephrotic syndrome (Luetscher and Johnson, 1954) fitted well with the thesis that sodium retention was related to high aldosterone production. However, in 1958, August *et al.*, showed that the administration of large doses of aldosterone to normal individuals does not lead to unremitting sodium retention. This led to the concept of 'escape' from the sodium-retaining effect of aldosterone. Not all patients without oedema are able to escape from the sodium-retaining effect of steroids (Mills, 1962). It may be assumed that the patients who are unable to escape in this way have some other abnormality. Patients in heart failure retain even more sodium when an electrolyte-active steroid is given. Although normal individuals given aldosterone will not retain sodium until they become oedematous, the presence of excess aldosterone production will add to the oedema caused primarily by another sodium-retaining mechanism.

The part played by glomerular filtration rate (GFR) dominated the picture for some time. During the phase of escape from the sodium-retaining effect of aldosterone the GFR frequently rises, and this has been considered by some workers to explain the mechanism of the escape (Barter, 1956). This explanation involves the supposition that the sodium in the few extra millilitres of plasma filtered per minute, passes down the tubules without change. Thus for each millilitre of plasma filtered 140 μ Eq of sodium is delivered to the tubules per minute. There is no reason to suppose, however, that this sodium would not be subjected to the processes that normally reabsorb more than 98 per cent of filtered sodium unless the tubules are normally working maximally to reabsorb sodium.

CHANGES IN BLOOD VOLUME AND COMPOSITION

The argument was finally settled when it was shown by de Wardener *et al.* (1961) that a sodium diuresis could be produced under circumstances in which the GFR was unmistakably reduced. This was achieved in dogs by inflating a balloon in the lower thoracic aorta so as to reduce the pressure in the renal arteries, while saline was rapidly infused intravenously. Subsequently workers confirmed this observation by using constriction of the aorta or the renal artery to reduce the blood pressure at the kidney (Levinsky and Lalor, 1963; Blythe and Welt, 1963).

Since sodium excretion can be increased despite high aldosterone levels and despite an appreciable fall in GFR, some other mechanism had to be sought which would presumably affect tubular reabsorption of sodium. The study

of de Wardener *et al.* (1961) and Mills *et al.* (1961) indicated that at the height of a sodium diuresis the rate of sodium excretion was not related to the GFR, the presence of the renal nerves, the blood volume or changes in the volume of extra-cellular fluid. As a result of cross-circulation experiments they concluded that the change in sodium excretion was the result of a change in the concentration of a circulating substance, which had a short half-life. However, as we shall see later, their data can equally well be explained in an entirely different way. Indeed, some of the negative correlations at the height of a sodium diuresis may be misleading when assessing the factors initiating the natriuresis.

The postulation of a circulating substance influencing sodium excretion led other workers to seek such a hormone. It was reported by Reçtor *et al.* (1968) that such a substance was present in plasma during a sodium diuresis and could be shown to influence sodium reabsorption from the proximal tubule of the rat by the micropuncture technique. Their subsequent failure to confirm their own observations caused them to withdraw the suggestion. The existence of a sodium diuretic hormone is still a possibility (Lichardus and Pearce, 1966) and indeed the observations of Cort and Lichardus (1963) are in favour of this. They and their colleagues believe they have demonstrated the existence of such a hormone, and their work on cats, in which they produced a diuresis by bilateral carotid artery occlusion, indicated that the substance might arise from inside the skull.

THE PRESSURE-SENSITIVE MECHANISM

An entirely different approach stems from the work of de Bono and Mills (1965). They occluded the left renal vein of dogs for five seconds in each minute for 20-minute periods. This produced a sharp rise in sodium excretion from the left kidney and no change from the right (Fig. 1). There were three important characteristics of this sodium diuresis: firstly, it was associated with a sharp fall in GFR; secondly, it persisted for 20 or even 40 minutes after the mechanical interference had stopped; and thirdly, it took place despite a large load of a sodium-retaining hormone (fludrocortisone). Renal vein occlusion initially causes a rise in renal vein pressure to the levels found at diastole in the renal artery within five seconds (Fig. 2). It fell to normal levels within one second of releasing the constriction on the vein. At the end of the 20 minutes of intermittent occlusion the renal haemodynamics had changed. Although the systemic blood pressure was essentially unchanged, the rate of rise of pressure inside the renal vein was much slower, indicating that the renal blood flow had decreased. The back-pressure produced by the venous occlusion increases transudation of fluid into the interstitial space and this could

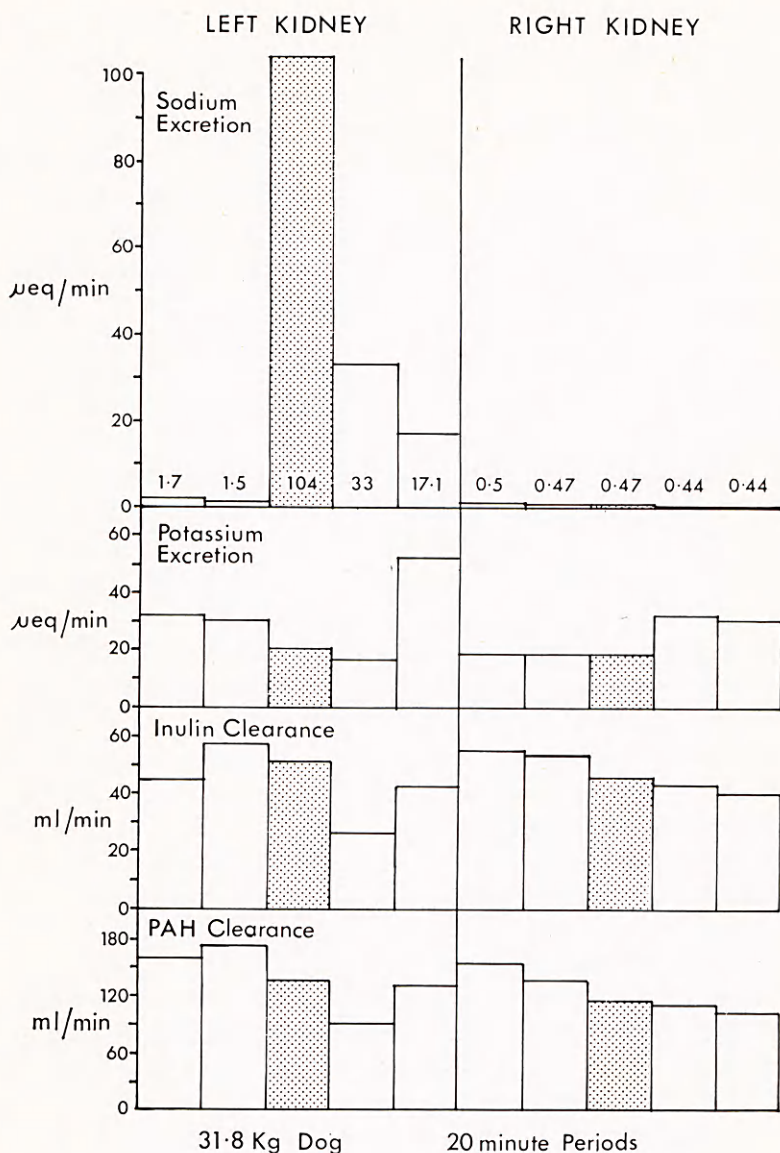


Fig. 1. Sodium and potassium excretion, inulin and PAH clearances for left and right kidneys, before, during, and after occlusion of the left renal vein for 20 minutes, in a 31.8 kg dog. Shaded columns are the occlusion period. (From de Bono & Mills, 1965.)

impede capillary flow without altering the pressure within the afferent arteriole.

It was presumed by de Bono and Mills (1965) that the rise in pressure within

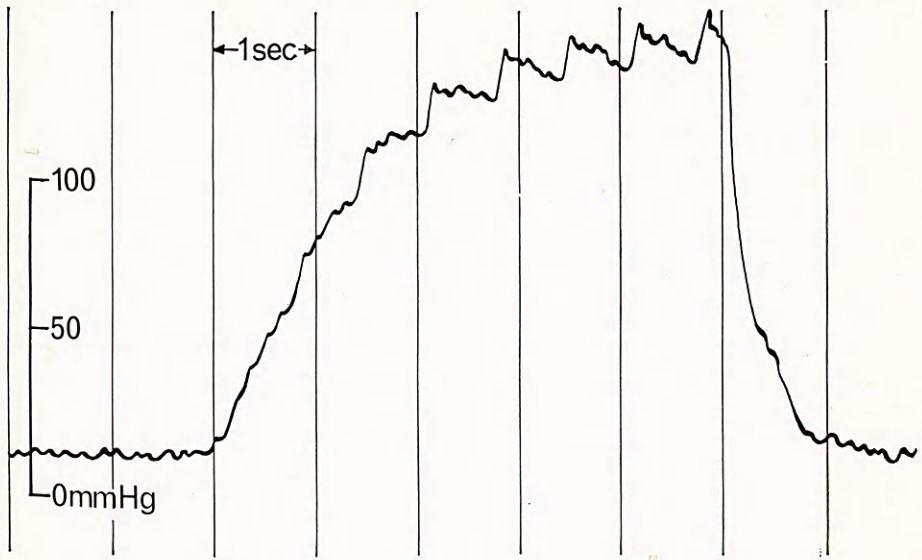


Fig. 2. Pressure in the renal vein during the occlusion (*see* Fig. 1), to show rate of rise of pressure and the fall when the occlusion is stopped. Note the pulsations coming through when the venous pressure approaches the arterial level. (From de Bono & Mills, 1965.)

the kidney operated to effect the sodium diuresis. A similar rise in pressure from the arterial side has been shown to cause natriuresis (Selkurt, 1951). This is more clearly shown in the perfused completely isolated dog kidney in which an increase in perfusion pressure increased sodium excretion without a change in GFR (Craig *et al.*, 1966). Sodium excretion is increased in an isolated kidney perfused by blood from a dog that receives a saline infusion, and the extent of the diuresis depends upon the perfusion pressure of the kidney (McDonald and de Wardener, 1965).

The isolated kidney perfused at constant pressure increases its sodium excretion when the blood is diluted with an electrolyte solution (Craig *et al.*, 1966; Nizet *et al.*, 1967; Berkowitz, 1967) but if the electrolyte solution contains dextran at a concentration iso-oncotic with plasma the rise in sodium excretion is very small (Nizet, 1968). It is obvious, therefore, that the isolated kidney, with no other organ in the circuit, can alter its excretion of sodium over a wide range, in response to dilution and changes in perfusion pressure.

The response of the kidney to changes in pressure can be either from the arterial or the venous side of the circulation. The effects of these two means of altering intrarenal pressure would coincide at the distal end of the afferent

arteriole and it would seem most probable that the pressure-sensitive site in the kidney which enables it to change its sodium excretion is at this point.

Because the afferent arteriole attenuates the pressure in the renal artery the pressure-sensitive site is acted upon by a pressure proportional to the blood pressure but inversely proportional to the tone in the afferent arteriole. If the blood pressure rises with no change in renal arteriolar tone, the pressure acting at the sensitive site will rise. If, however, the rise in blood pressure is brought about by generalised vasoconstriction which involves the renal vessels, the pressure acting at the sensitive site may remain the same or even decrease if the renal vessels are disproportionately vasoconstricted. If the increased tone goes beyond a certain point the filtration pressure will fall and the GFR will be lowered. This situation is well exemplified by patients with subarachnoid haemorrhage. In this condition hypertension occurs and its severity is related to the degree of elevation of CSF pressure. It has been shown by James (1968) that the elevation of blood pressure is related to sodium retention and, in the more severely affected patients, the rise in blood pressure is very great and associated with a fall in GFR. The elevation of blood pressure under these circumstances, although in part due to an increase in cardiac output, is, to an appreciable extent, due to constriction of the peripheral vessels. James and Wise (1969) demonstrated that denervation of one kidney in dogs prevented the fall in sodium excretion from that kidney as the blood pressure rose with elevation of the pressure in the CSF. The kidney with intact nerve supply showed the usual decrease in sodium excretion.

POSTURAL HYPOTENSION

The opposite state of affairs exists in patients with postural hypotension associated with defective vascular reflexes. It has been known for some years that these patients have abnormally low aldosterone excretion when they are on a low salt diet (Bartter *et al.*, 1959) and that their renal handling of sodium is abnormal (Wagner, 1957; Shear, 1963). However, administration of a sodium-retaining steroid will not restore the handling of sodium to normal (Wilson *et al.*, 1969). When they lie down at night they excrete more sodium, whereas normal individuals retain sodium by night. During the day, especially if they are up and about, they excrete less salt. It has been shown (Wilson *et al.*, 1969) that the aldosterone production rate by these patients on a normal salt intake is either at the lower end of the normal range or below it and rises only modestly on sodium restriction. Infusions of noradrenaline that raise the blood pressure have very little effect on aldosterone production and may cause a sodium diuresis instead of the usual sodium retention.

A major factor in the regulation of aldosterone production is the rate of renin release by the kidney. Renin is produced by the juxta-glomerular (JG) cells situated at the distal end of the afferent arteriole. Renin production is in part related inversely to the pressure acting at the JG cells. This pressure is determined by the relationship between the blood pressure and the tone on the afferent arteriole. It is probable that renin release is stimulated by sympathetic drive on the renal vessels (Bunag *et al.*, 1966; Vander, 1965) and the renin so released is probably more than would be expected by the pressure changes alone. In patients with postural hypotension the arteriolar tone is abnormally low, hence the fall in blood pressure when they stand up. Plasma renin is abnormally low in these patients and is not easily raised by salt restriction (Gordon *et al.*, 1967). This fits in with the postulate that the lack of tone on the afferent arteriole allows a greater than normal pressure to act at the JG cells because attenuation of the blood pressure is markedly less than normal. The higher pressure at the JG cells suppresses the secretion of renin and, in turn, the angiotensin level falls and there is less stimulation of aldosterone production.

The pressure-sensitive site in the kidney that affects sodium excretion appears to be in the same region as the JG cells but this does not necessarily imply that renin is playing a part directly in the regulation of sodium excretion by the kidney. In patients with postural hypotension the lack of tone on the afferent arteriole in the kidney means that the pressure at the pressure-sensitive site moves in parallel with the blood pressure. Tipping the patient towards the vertical causes a fall in blood pressure and sodium retention. This can be made use of in treating the patients because if the head of the bed is raised so as to produce a 14 degree tilt they will not lose sodium excessively at night (Wilson *et al.*, 1969). As a result the blood volume remains more normal and they are less likely to fall unconscious when they walk about. The low level of aldosterone is an additional reason for salt loss. However, administration of fludrocortisone is very liable to cause potassium loss unless they sleep on a tilted bed (Wilson *et al.*, 1969). This suggests that tilting the bed promotes reabsorption of sodium in the proximal tubule so that less reaches the distal tubule where fludrocortisone as well as aldosterone promote reabsorption of sodium in exchange for potassium.

Patients with postural hypotension, therefore, are in the opposite situation to those with subarachnoid haemorrhage. The former have normal or low blood pressure but lose sodium because the pressure-sensitive site is not protected by tone on the afferent arteriole. The latter have hypertension and sodium retention because the pressure-sensitive sodium controlling mechanism is understimulated as a result of the excessive tone on the renal arterioles.

VASCULAR REFLEXES

Under normal conditions a normal blood pressure is maintained in both animals and man by the balance between the cardiac output and the peripheral arteriolar resistance. Vascular reflexes and circulating vasoactive substances adjust the peripheral tone according to changes in circumstances. These changes may be local, as in secretion by salivary glands or pancreas or in the vasodilatation of active muscles; or they may be general, as in the vasoconstriction after haemorrhage. The regulatory mechanisms are extremely complex but some of the reflexes are well known. The arterial baroreceptors in the carotid arteries and aortic arch have long been known to play a major role in regulation of blood pressure.

The effects of constriction of the carotid arteries depend upon the species and the degree of constriction. Carotid artery constriction causes a rise in the blood pressure in all species studied. In the cat, complete constriction leads to natriuresis (Cort *et al.*, 1969) but in the dog this increased sodium excretion is less predictable. With progressive partial carotid artery constriction in the dog there is a phase of sodium retention before the diuretic phase is reached (Mills, 1968). Although the details of these mechanisms have not been worked out, it is known that the elevation of the blood pressure has two components: one is vasoconstriction, especially in the splanchnic bed (Heymans and Neil, 1958), and the other is the increase in cardiac output. Elevation of the blood pressure without an increase in tone on the renal afferent arteriole would raise the pressure beyond the afferent arteriole in the kidney. In this situation sodium diuresis occurs. Conversely, elevation of blood pressure by vasoconstriction alone causes a fall in pressure beyond the renal afferent arteriole. As we saw in the case of raised CSF pressure, this causes sodium retention which can be abolished experimentally by denervation of the renal artery.

Another vascular reflex which has a bearing on renal function is that related to stretch of the right atrium. In the early stages of haemorrhage the blood pressure remains unchanged until about 20 per cent of the blood volume is lost. During this phase, Henry *et al.* (1968) have shown that the rate of firing of the aortic arch baroreceptors is unchanged when integrated over short periods of time (i.e. taking into account that there is an increased heart rate). However, the rate of firing of receptors in the right atrium falls with even small reductions in blood volume. As soon as the blood pressure falls, the firing of the aortic baroreceptors falls. It is well known that sodium retention occurs with haemorrhage even when there is no fall in blood pressure.

A second study of right atrial stretch in relation to vascular reflexes was carried out by Mills and Osbaldiston (1968). After occluding both common carotid arteries in dogs, they showed that stretch of the right atrium caused a

sharp fall in blood pressure of up to 50 mm Hg (hypertension had been caused by the carotid occlusion) which caused no fall in renal blood flow or inulin clearance; the sodium excretion tended to rise rather than fall. This effect of right atrial stretch was abolished by vagal section. They concluded that the fall in blood pressure with stretch of the right atrium was caused by vasodilatation involving the renal vessels. If the fall in blood pressure is associated with a comparable decrease in renal afferent arteriolar tone, the pressure beyond the afferent artery would be unchanged.

THE MECHANISM OF THE SODIUM DIURESIS

There are two main views on the means by which a change in sodium excretion is brought about. Either there is a change in the concentration of a circulating substance other than aldosterone, or an intrarenal mechanism is involved.

Circulating Substance Theory

This view is particularly held by de Wardener (1969) who places great emphasis on the experiments he and his colleagues have carried out in which they expanded the blood volume of dogs with blood from a reservoir which was already in equilibrium with the circulating blood (Bahlmann *et al.*, 1967). This produced a natriuresis. By denervating one renal artery and using a clamp to prevent any rise in blood pressure to that kidney they showed that an increase in sodium excretion still occurred. They concluded that a change in the blood must have occurred to explain the natriuresis. More recently they have shown that if the blood passes over frog's skin in an appropriate cell, expansion of the blood volume causes a fall in the active sodium transport by the skin, as measured by the short-circuit current (Nutbourne *et al.*, 1970). It is known that frog's skin increases its sodium transport with a rise in the concentration of circulating catecholamines (Bastide and Jard, 1968) which is within the physiological range. It is possible, therefore, that the effects of blood volume expansion could be explained by a fall in the concentration of circulating catecholamines. This would have a direct effect on renal afferent arteriolar tone and, therefore, alter the intrarenal pressure-sensing mechanism. Indeed, the work of McDonald and de Wardener (1965) suggests that a similar explanation applies to the perfused dog's kidney which receives a saline infusion, because they showed that the extent of the diuresis of the external kidney depended upon the pressure used for perfusion.

An entirely different series of experiments was conducted by Pearce *et al.* (1969). They expanded the blood volume of rats in a variety of ways. Sodium depleted rats had only a small sodium diuresis on expansion of the blood volume with equilibrated blood. Rats treated with DOCA had a greater

increase in sodium excretion when treated in the same way. If sodium depleted rats were cross-circulated with DOCA-treated rats and then had their blood volume expanded, they had a greater natriuresis; but the DOCA-treated rats whose blood volume was expanded after the cross-circulation had no less sodium diuresis. This suggested that the DOCA-treated rats had a circulating substance that enhanced sodium excretion. However, these results could be due to changes in circulating vasoactive substances rather than a substance acting directly on the renal tubules.

Against the theory that the major factor in natriuresis is a circulating substance is the study of de Bono (1968). He wrapped one kidney of a dog with thin latex tubing about one inch wide, in a figure of eight. Saline was then infused rapidly intravenously (1 ml/kg/min). Although there was a comparable rise in renal blood flow and inulin clearance on the two sides, the wrapped kidney had a very small sodium diuresis compared to the untouched one (Fig. 3). However, when frusemide was given intravenously there was a five-fold rise in sodium excretion from the wrapped side. We may conclude that any change in the concentration of a circulating substance produced by the saline infusion would affect both equally since they had comparable rises in blood flow. It is most unlikely, therefore, that such a circulating substance is the dominant factor in the sodium diuresis. Furthermore, it is probable that the pressure-sensitive mechanism in the kidney operates by sensing a change in transmural pressure. This would be reduced by the latex pressing on the outside as the vasodilatation caused by the saline infusion allowed greater internal pressure beyond the afferent arteriole.

The Intrarenal Theories

There are two separate theories: the first is that the response in the kidney is due to a physical change. The second is that the sodium excretion is controlled by the release of an intrarenal hormone in response to changes in pressure at a site distal to the afferent arteriole.

There is general agreement that saline infusion changes the rate of sodium reabsorption in the proximal renal tubule. This was first shown by micro-puncture techniques by Dirks *et al.* (1965). However, this can be abolished by a constriction of the aorta or renal artery severe enough to lower the GFR by more than 50 per cent (Brenner *et al.*, 1968) or by partial constriction of the supradiaphragmatic vena cava (Cirkseña *et al.*, 1966). These studies show that the effects of vascular expansion with saline are abolished if the pressure to the kidney is low enough. The results reinforce those of McDonald and de Wardener (1965) mentioned above.

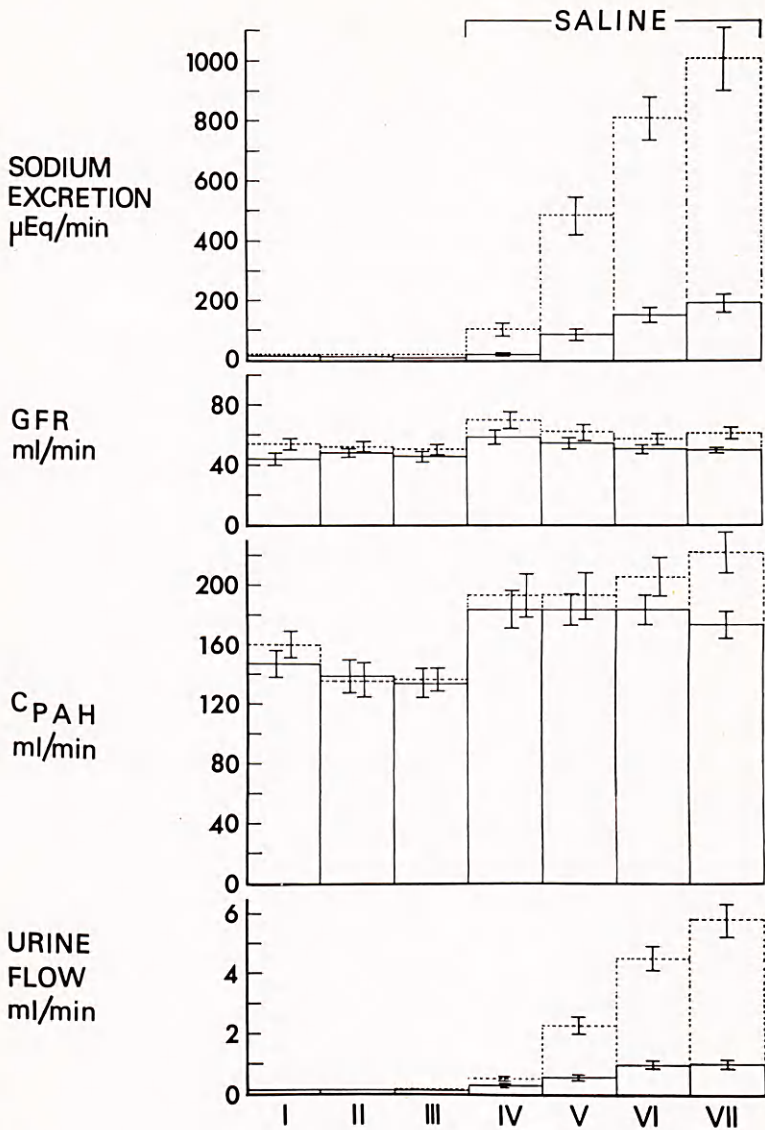


Fig. 3. The sodium excretion, GFR, PAH clearance and urine flow in three control 20 min periods and four periods of saline infusion at 1 ml/kg/min. The mean values for seven experiments are shown. The bars represent the standard errors of the means. The solid lines represent the left kidney wrapped with latex and the dotted lines the untouched right kidney. (From de Bono, 1968.)

It was postulated by Rector *et al.* (1966) that a change in the geometry of the renal tubule as a result of altered blood and interstitial pressures inside the kidney was the operative factor in altering tubular reabsorption of sodium. The more careful studies of Brenner *et al.* (1968) have established that this is not so. The work of Stahl (1965) showed that intrarenal interstitial pressure is raised as much by ureteric occlusion as by partial renal vein occlusion. These two mechanisms produce opposite effects on sodium excretion.

The final proof that alterations of tubular geometry or pressure do not play an important role in controlling sodium excretion has been given by the work of Morgan and Berliner (1969). They perfused segments of proximal tubule with solutions of known composition under conditions of increased and decreased intratubular pressure and showed no significant alteration in sodium reabsorption by the tubule. In the same experiments expansion of blood volume had a significant effect on the sodium reabsorption of the same tubules.

An alternative intrarenal mechanism has been presented by Windhager *et al.* (1969). They infused solutions into the capillaries surrounding the proximal tubule and by micropuncture estimated the rate of tubular sodium reabsorption. With 8 per cent dextran in the solution infused the rate of sodium reabsorption was faster than with 4 per cent dextran or saline. They suggest that filtration at the glomerulus raises the protein concentration in the blood passing to the capillaries surrounding the proximal tubules, and the high oncotic pressure in the capillaries then determines the rate of sodium reabsorption across the interstitial space from the proximal tubule. When saline is infused into an animal the plasma protein concentration falls and this would produce a lowered oncotic pressure to act on the proximal tubule. Although such a factor undoubtedly plays a part, it can be overcome by some other factor, as shown by Howards *et al.* (1968) who infused 25 per cent albumin and showed that the expansion of the blood volume overcame any local effect of the high oncotic pressure in the kidney and produced a decrease in the sodium reabsorption by the proximal tubule. The postulate of Windhager *et al.* would not explain the natriuresis caused by expansion of the blood volume by blood.

Work from Berliner's laboratory (Brenner *et al.*, 1968) showed how rapid is the rate of change of tubular handling of sodium. When the aorta above the renal artery was partially clamped the increase in reabsorption of sodium in the proximal tubule could be measured in less than one minute and sometimes within 30 seconds. The same time scale operated when the clamp on the aorta was released and there was a decrease in sodium reabsorption. The rapidity of this response makes it unlikely that a circulating substance is responsible

and also unlikely that the macula densa operates a feedback inside the kidney. However, it is compatible with the release inside the kidney of a hormone acting on sodium transport in the proximal tubule.

The mechanisms involved in the concept of the regulation of sodium excretion by an intrarenal pressure-sensitive site are illustrated in Fig. 4. If one imagines the pressure in the main renal artery to be 100 mm Hg, the pressure at the distal end of the afferent arteriole (in the region of the JG cells) might be 70 mm Hg. The filtration pressure in the glomerulus might be 50 mm Hg and the pressure in the efferent arteriole 40 mm Hg (Fig. 4*a*).

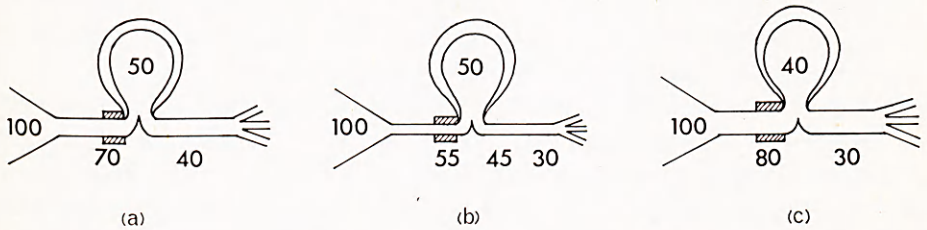


Fig. 4. Schematic representation of the intrarenal pressure-sensing mechanism. Figure 4(*a*) depicts the normal state, 4(*b*) the early stages of haemorrhage, and 4(*c*) either autonomic dysfunction with loss of renal arteriolar tone or vasodilatation during saline infusion with concomitant slight reduction in GFR. (From Mills, 1968.)

During haemorrhage, vasoconstriction occurs (Fig. 4*b*). In the early stages the blood pressure in the main renal artery would be maintained at 100 mm Hg. The vasoconstriction in the afferent arteriole would attenuate the pressure and reduce it to perhaps 55 mm Hg at the JG cells. However, the constriction of the efferent arteriole would impose a greater resistance to flow and for some time might maintain the filtration pressure at 50 mm Hg. The attenuation of pressure in the efferent arteriole might reduce it to 30 mm Hg by the time the arteriole divides into the peritubular capillaries. In this situation the pressure-sensing cells would record a decreased pressure while the GFR would be maintained. Further vasoconstriction would, of course, reduce the GFR as well as the pressure at the distal end of the afferent arteriole.

Figure 4(*c*) represents the situation in patients with autonomic dysfunction and postural hypotension. Both arterioles are now widely dilated. The afferent arteriole imposes little attenuation and the pressure at the region of the JG cells might be 80 mm Hg. However, the dilated efferent arteriole, by imposing little resistance to flow, might even allow the filtration pressure to drop to 40 mm Hg. Here the pressure-sensitive site is exposed to a higher pressure than usual without a rise in GFR and perhaps a slight fall. This is also likely to occur when the blood is diluted by saline infusion because the

change in viscosity of the blood after filtration leads to an appreciable rise in resistance to flow when the arterial haematocrit is normal, but has little effect when the haematocrit is lowered by dilution with a solution with negligible oncotic pressure (Nashat *et al.*, 1969). In FIG. 4c we see the situation that can produce a sodium diuresis in spite of lowering of GFR.

THE EFFECTS OF RENAL EXTRACTS

It has been known since 1940 that crude renin extracts of kidneys when infused intravenously into rabbits cause a marked increase in urine flow (Pickering and Prinzmetal, 1940). Elevation of blood pressure by infusion of large doses of angiotensin have the same effect (Langford and Pickering, 1965). The response to angiotensin infusion depends upon the dose. Small doses cause sodium retention when the dose is insufficient to raise the blood pressure (Barraclough *et al.*, 1967; Louis and Doyle, 1965). Larger doses cause a sodium diuresis with the greater elevations of blood pressure. This latter effect may in part be mediated by the direct effect of angiotensin on the vasomotor centre in the medulla (Lowe and Scroop, 1969; Joy and Lowe, 1969). Since angiotensin has opposite effects on sodium excretion, depending upon the dose, it seems unlikely that it acts on the renal tubule to control sodium excretion.

More recently, crude renal extracts have been infused into the renal artery of dogs (de Bono *et al.*, 1969; Mills *et al.*, 1969). The infused side had an increased sodium excretion, whereas the opposite side had a minimal or no natriuresis. Extracts treated at pH 2.5 for one hour lost most of their natriuretic activity but retained the action of renin as shown by the rise in blood pressure. Further evidence that renin is not the intrarenal natriuretic hormone has been brought forward by Bartter and Mills (1970).

CONCLUSIONS

Changes in glomerular filtration rate and aldosterone production may, under appropriate conditions, alter the rate of sodium excretion. Under different circumstances sodium diuresis can be produced despite a fall in GFR and in the face of large amounts of sodium retaining steroids. It is apparent that some other mechanism must be playing a major role in the control of sodium excretion. Expansion of blood volume with saline, blood, albumin or dextran solutions will all increase sodium excretion provided they do not cause heart failure. Dilution of blood without vascular expansion in the whole animal, or in the isolated kidney infused at constant pressure, will also cause natriuresis.

Changes in haemodynamics or interstitial pressure inside the kidney alter its rate of sodium excretion. From all these studies it may be postulated that

sodium excretion is controlled by the change in the concentration of a circulating substance or by an intrarenal pressure-sensitive mechanism. The evidence against a circulating substance playing a major role (unless it has vasoactive properties, or originates in the kidney itself) seems to suggest that the intrarenal mechanism is the more likely. The response to dilution of the blood in an isolated kidney system could itself operate by a pressure-sensitive mechanism. The lowered viscosity of the blood would alter the resistance to flow within the arteries and so change the distribution of pressure along the vessels. Since pressure on the outside of the kidney can lessen the rate of sodium excretion it seems that the pressure in the kidney is being sensed across the vascular wall. The JG cells do that, and although they are known to produce renin it is not impossible that they produce something else as well.

The explanations for the natriuresis based on physical factors alone seem either not to be true or to have only a limited application (e.g. changes in oncotic pressure). The evidence supports the view that the kidney senses the difference between the intravascular pressure and that of the interstitium at a point distal to the main attenuating system (the afferent arteriole). In this way it regulates sodium excretion in terms of flow at the sensing site. The blood pressure alone may give no indication of the pressure at this sensing region because the latter pressure also depends on neural and humoral factors controlling the tone on the afferent arteriole.

The fact that GFR and sodium excretion can to some extent be controlled independently is in favour of the view that the pressure-sensing cells are located between the afferent and efferent arterioles. In this way they would respond, in effect, to the local blood flow before it is altered by glomerular filtration.

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