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Personal Opinion

Renal determinants of the salt sensitivity of blood pressure

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Introduction

The evidence that sodium plays an important pathophysiological role in the development of hypertension comes from various sources. Epidemiological studies such as the Intersalt Study [1] have demonstrated a positive interpopulation relationship of 24-h urinary sodium excretion with blood pressure and the importance of salt intake in determining the rise of blood pressure occurring with age [1]. In addition, a large amount of experimental and clinical studies has emphasized the crucial role of sodium in the regulation of blood pressure and the implications of an abnormal sodium balance in the development of hypertension in animal models as well as in humans [1–4].

Despite this evidence, the potential benefits of a population-scaled reduction of salt intake to lower blood pressure and hence to reduce the risk of cardiovascular diseases, and perhaps other diseases such as osteoporosis, cancer, and pulmonary diseases [3], are still a matter of intensive debate. Several meta-analyses have concluded that salt reduction in the general population produces a weak effect on blood pressure in normotensive subjects and only a slightly greater reduction of blood pressure (ranging between −3.7 and −4.9 mmHg in systolic and −0.9 and −2.6 mmHg in diastolic pressure) in hypertensive patients [5–7]. In the most recent meta-analysis, Graudal *et al*. [7] have even suggested that salt restriction could have a potentially deleterious effect on hormonal and lipid profile. In this respect, Alderman *et al*. found in a population-based study an inverse correlation between salt intake and all-cause and cardiovascular mortality [8]. This observation of course gave rise to many criticisms [9,10].

Salt sensitivity: a controversial concept

The role of salt intake as a determinant of individual blood pressure levels is certainly very variable. Thus, in most individuals a very wide range of salt intake is accompanied by only a modest and transient change in arterial blood pressure as one would expect from the pressure–natriuresis relationship that dominates the long-term control of blood pressure [11].

Kawasaki *et al*. [12] and later on Weinberger *et al*. [13] were among the first to recognize the heterogeneity of the blood pressure response to salt and to develop the concept of salt sensitivity and salt resistance in humans. Initially, Weinberger *et al*. [14] defined salt sensitivity arbitrarily as an increase in mean arterial pressure greater than 10% with the high-salt diet compared with the low-salt period, subjects being submitted to extreme changes in sodium intake (from 10 to 250 mmol per day) for 1 week. Subsequently, various experimental protocols have been used to test the salt sensitivity of blood pressure in humans, including an acute protocol in which patients are salt-loaded with an intravenous infusion of saline and salt-depleted with the administration of frusemide [14]. In addition, the definition of salt sensitivity tended to vary between studies being sometimes defined as an increase in mean arterial pressure of 3 to 10% or greater than 10 mmHg. Despite the variety of the definitions and protocols used to test salt sensitivity, several findings were consistently observed: hypertensive patients are more frequently salt sensitive than normotensive subjects and the prevalence of salt sensitivity is increased in older individuals, black populations, and patients with a low-renin hypertension such as diabetics [13]. The menstrual cycle does not have any significant impact on the blood pressure response to salt, at least in normotensive women [15].

The heterogeneity of the blood pressure response to salt has been further emphasized by an interesting study conducted in chimpanzees which demonstrated

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that salt added progressively to the diet during 20 months causes a significant rise in systolic, mean, and diastolic blood pressures. The strength of this study is that in a control group from the same colony reared under exactly the same conditions except for a low-sodium diet, blood pressure did not rise. Moreover, the blood pressure changes reversed completely after cessation of salt. Most interestingly, some animals exhibited a large blood pressure increase on a high-salt diet whereas others had only a small or no rise in blood pressure. These observations clearly suggest that individual, possibly genetic, factors also modulate the effect of salt on blood pressure [16].

In recent years, several important questions have been raised regarding the validity of this clinical concept. The first concerns the arbitrary dichotomization of the population. The salt-induced changes in blood pressure with salt are in fact normally distributed and hence there is no evidence for a bimodal distribution, and a salt-sensitive population cannot be clearly defined. The second major criticism regards the reproducibility of the determination of salt sensitivity [17,18]. Thus, whereas Campese *et al.* [19] maintain that salt sensitivity is not a random, but a reproducible and persistent phenomenon over time when assessed according to rigorous protocols, Zoccali *et al.* [20] found that the determination of salt sensitivity has a rather low reproducibility. Finally, several technical aspects of the procedure itself have been questioned, including the duration of the changes in salt intake and the adequacy of the method used to measure blood pressure. In this respect, it has been suggested that acute changes in sodium balance may not adequately reflect the situation obtained with long-term changes in sodium intake and that ambulatory blood pressure monitoring could be a more reliable way of measuring the salt-induced changes in blood pressure [21–23].

Renal determinants of salt sensitivity

Guyton [11] first described in dogs the pressure–natriuresis curve, which reflects the relationship between salt balance and systemic blood pressure in normal and pathological conditions. According to his hypothesis, the pressure–natriuresis curve has always to be affected in hypertension whatever the cause initiating the hypertensive process [11]. This underlines the prominent role of water and sodium excretion by the kidneys in determining the long-term level to which blood pressure is regulated. Kimura and Brenner [24] have extended this approach and described the various pressure–natriuresis curves in sodium-sensitive and sodium-resistant forms of secondary hypertension. In addition, they proposed three major renal mechanisms leading to the development of hypertension: an increased pre-glomerular vascular resistance, a decrease in whole kidney ultrafiltration, and an increase in tubular sodium reabsorption. They suggest that pre-glomerular vasoconstriction leads to a salt-resistant hypertension whereas a reduced nephron mass and alterations of renal sodium handling result in the development of salt-sensitive forms of hypertension (Figure 1). More recently, Johnson and Schreiner [25]

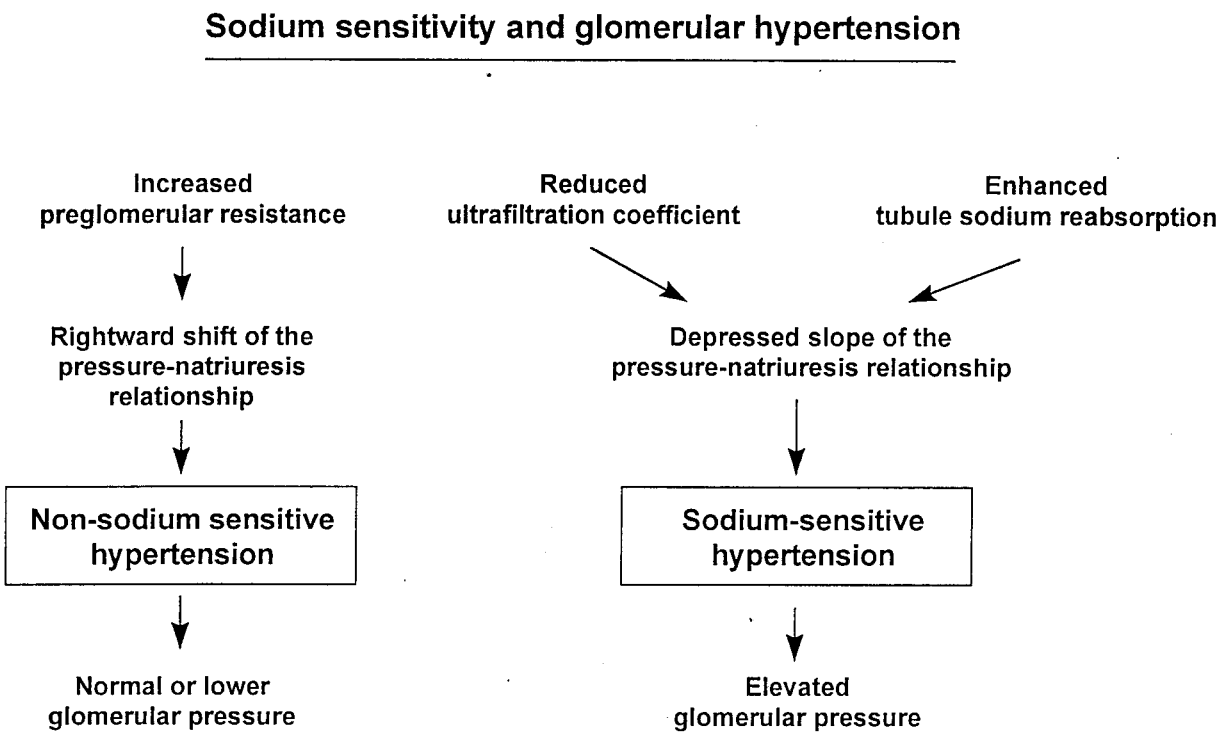

Fig. 1. Hypothetic renal mechanisms of salt sensitivity and their potential implications for intraglomerular pressure. Adapted from ref [24].

have emphasized the role of microvascular injury and tubulointerstitial fibrosis in the development of salt-sensitive hypertension by shifting the pressure–natriuresis curve to the right. Thus, they have shown that transient angiotensin II [26] and phenylephrine infusions [27] can induce renal microvascular injury and tubulointerstitial fibrosis and salt-dependent hypertension even when the hyperactivity of the sympathetic or renin–angiotensin system is no longer engaged. Similar renal injuries have actually been documented in several experimental models (cyclosporin-induced hypertension or ageing) and clinical situations of salt-sensitive hypertension.

These various hypotheses, together with the results of renal transplantation experiments in animals [28] and humans [29], point out the kidney as the key determinant of the blood pressure response to salt. Yet salt sensitivity is definitively a multifactorial phenomenon involving extrinsic, essentially hormonal, as well as intrinsic renal tubular and haemodynamic mechanisms modulated by genetics factors. The respective contribution of each of these mechanisms, which will be discussed below, is often difficult to dissociate, since several of these factors are closely linked.

Hormonal response to salt and salt sensitivity

Several hormonal and autocrine systems have been involved in the pathophysiology of salt sensitivity including the renin–angiotensin–aldosterone system [30–32], the sympathetic nervous system [33–35], insulin [36–38], bradykinin [39,40], atrial natriuretic peptides [21,41], nitric oxide [42,43], and endothelin [44]. Suppression of the renin–angiotensin–aldosterone system is one important mechanism for both the immediate and longer-term increase in sodium excretion following an increased sodium intake. Hall *et al.* [45] have elegantly demonstrated in the dog that when the activity of the renin–angiotensin system cannot be modulated, blood pressure becomes salt dependent [45]. In the line of this initial observation, several investigators have found that renin activity is inappropriately suppressed in patients whose blood pressure increases on a high-sodium diet and that the blunted renin response correlates with a diminished salt-induced renal vasodilatation [31,32]. Moreover, blockade of the renin–angiotensin system has been shown to partly correct the impaired renal haemodynamic response to sodium [32]. In the same context, in hypertension due to hyperaldosteronism with no possibility to modulate circulating aldosterone levels, blood pressure is salt sensitive [24].

There is also some evidence that the activity of the sympathetic nervous system (SNS) modulates the blood pressure response to salt. Physiologically, an increase in salt intake suppresses the activity of the SNS. Salt sensitivity has been linked to an enhanced sympathetic activity and to increased circulating catecholamines [33–35]. Others have found an increase in the ratio of noradrenaline to dopamine secretion in salt-sensitive hypertension [46]. The role of the sympathetic nervous system appears to be particularly important in the pathogenesis of obesity-induced hypertension [47]. Indeed, there is evidence that the pressure natriuresis relationship is altered in obese subjects and can be corrected by losing weight [37]. In obesity, the altered pressure–natriuresis relationship appears to be caused primarily by an increased tubular sodium reabsorption, since glomerular filtration rate and renal plasma flow tend to be increased [47]. It has been suggested that insulin resistance and the compensatory hyperinsulinaemia mediate the obesity-induced hypertension *via* an activation of the sympathetic nervous system. Thus, increased serum insulin levels have been measured in Dahl salt-sensitive rats even before the development of hypertension [48] and insulin resistance exacerbated by a high-salt intake has been found in salt-sensitive hypertensive subjects [38]. More recent data, however, suggest that the development of salt-sensitive hypertension in obese patients is not due to hyperinsulinaemia or insulin resistance but rather to an activation of the renin–angiotensin and sympathetic nervous systems independent of insulin, combined with altered intrarenal physical forces which compress the renal medulla and may decrease tubular sodium reabsorption [47].

More recently, evidence has been provided suggesting that the endothelin-B (ETB) receptor also contributes to the regulation of renal sodium handling in the rat [44]. Thus, rats that are functionally ETB deficient exhibit extreme salt-sensitive hypertension which appears to be due to an abnormally high activity of the epithelial sodium channel in the renal collecting duct. The results of this study suggest that in the distal nephron, endothelin counterbalances the renin–angiotensin system in regulating the activity of the epithelial sodium channel.

Renal haemodynamic response to salt

The renal haemodynamic response to changes in sodium intake has been studied by several investigators in salt-sensitive and salt-resistant hypertensive patients, and so far results have been quite concordant [31,32,49]. In normotensive controls and salt-resistant hypertensive patients, a high-sodium intake induces an increase in renal blood flow and glomerular filtration rate leading to no change or a slight decrease in filtration fraction. In contrast, the renal haemodynamic response to salt loading in salt-sensitive patients or subjects is characterized by a decrease in renal blood flow and no change in glomerular filtration rate; hence filtration fraction, an indirect marker of intraglomerular pressure, increases. This particular response of salt-sensitive subjects suggests an increase in pre- and post-glomerular vasoconstriction and has

been attributed to an inadequate regulation of the renin–angiotensin system [32].

Renal sodium handling in salt sensitivity

Although increased tubular sodium reabsorption is generally accepted as one of the crucial steps in the genesis of essential hypertension, the renal tubular abnormality(ies) leading to this increased reabsorption has(ve) not yet been elucidated. Recently, the molecular mechanisms of three rare Mendelian forms of hypertension in humans have been elucidated: Liddle's syndrome, the syndrome of apparent mineralocorticoid excess, and glucocorticoid-remediable aldosteronism [50]. In each of these rare diseases, an increased tubular sodium reabsorption by the distal nephron has been documented, leading to a salt-sensitive form of hypertension and confirming the importance of an altered renal sodium handling in the development of hypertension. However, highly prevalent forms of essential hypertension are probably due to different mechanisms although one cannot exclude the possibility that subtle alterations of sodium transport in the distal nephron participate to their pathogenesis. In fact, patients with essential hypertension are devoid of primary disturbances in distal sodium reabsorption. In contrast, there is increasing experimental and clinical evidence that an increased sodium reabsorption in the renal proximal tubule contributes to the development of hypertension [51].

Using lithium clearance as a marker of renal sodium handling by the proximal tubule, we have demonstrated previously in rats [52] as well as in humans [53] that the renal fractional excretion of lithium (FE_{Li}) varies in close relation with the fractional excretion of sodium (FE_{Na}). Thus, in normotensive subjects and animals receiving a high-salt diet, the FE_{Li} increases markedly and in proportion with the FE_{Na}, leading to a steep FE_{Li}/FE_{Na} relationship. In hypertensive subjects and various models of hypertension in the rat, this FE_{Li}/FE_{Na} relationship was significantly flatter, suggesting that on a high-sodium diet, hypertensive animals and humans were not adequately reducing their proximal sodium reabsorption to get rid of the excess of salt. More recently, we have put forward the hypothesis that hypertensive patients able to increase their FE_{Li} on a high-sodium intake are those with the blood pressure insensitive to salt [54]. In contrast, salt-sensitive hypertensive patients would be those exhibiting an inability to adapt their proximal sodium reabsorption on a high or low sodium diet (Figure 2).

To investigate this hypothesis, we have evaluated prospectively the changes in blood pressure, renal haemodynamics, and segmental renal sodium handling in 38 hypertensive patients and 12 normotensive controls studied after 1 week of a high- and low-sodium diet [54]. In order to avoid any arbitrary definition of salt sensitivity, hypertensive patients were distributed into three tertiles according to the changes in blood pressure from a high- to a low-salt diet. Interestingly, patients in the first tertile, i.e. those with the smallest change in pressure disclosed a pattern of adaptation of proximal sodium reabsorption comparable to that of normotensive controls. In contrast, the most salt-sensitive patients of the third tertile had an inverse pattern with a high FE_{Li} on low salt and a lower FE_{Li} on high salt, suggesting an inappropriate modulation of proximal sodium reabsorption (Figure 3). The blood pressure response to salt correlated positively with age and with the changes in FE_{Li} and the variations of proximal sodium reabsorption were not related to the changes in renal haemodynamics.

Surprisingly, the renin response to salt was not different in the three tertiles, suggesting that the renin–angiotensin system is not a major determinant of salt sensitivity. However, one has to be cautious

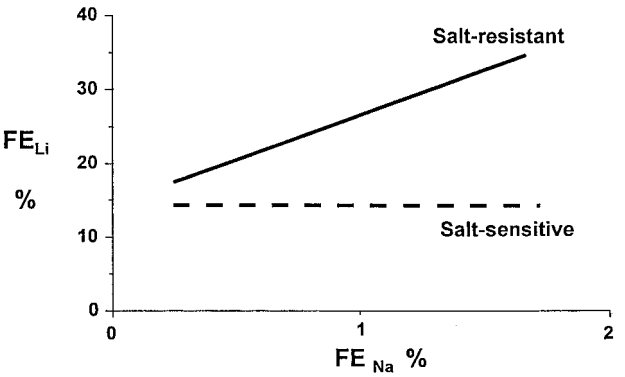

Fig. 2. Schematic representation of our hypothesis suggesting that salt-resistant subjects or patients increase their FE_{Li} when receiving a high-salt diet whereas salt-sensitive patients are characterized by an inadequate proximal tubular response with no increase in FE_{Li}.

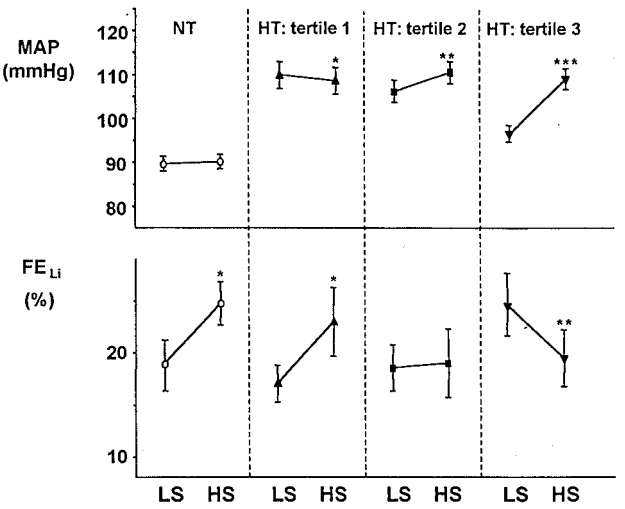

Fig. 3. Mean arterial pressure (MAP) and fractional excretion of lithium (FE_{Li}) on a low-(LS) and high-salt (HS) diet. NT: normotensive subjects, $n=12$. HT: hypertensive patients divided in tertiles according to their blood pressure response to salt ($n=12$–13). $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ *vs* LS. Note that salt-resistant patients of the first tertile exhibit salt-induced changes in FE_{Li} which are comparable to those of normotensive controls, whereas salt-sensitive patients have an inverse pattern of FE_{Li} changes.

with this interpretation because one cannot exclude the possibility that the intrarenal renin–angiotensin system modulates the proximal tubular response to salt [55]. More specific studies, including a specific blockade of the renin–angiotensin system, should be conducted using the same protocol to assess in more details the role of the renin–angiotensin system in regulating the tubular response to salt in salt-resistant and salt-sensitive hypertensive patients. In support of our general hypothesis, Barba *et al.* [56] have found that salt-sensitive normotensive men have a greater absolute proximal reabsorption of sodium on a high salt diet when compared with salt-resistant men. Taken together, these findings suggest that sodium handling by the proximal tubule is indeed an independent determinant of the sensitivity of blood pressure to salt in hypertension.

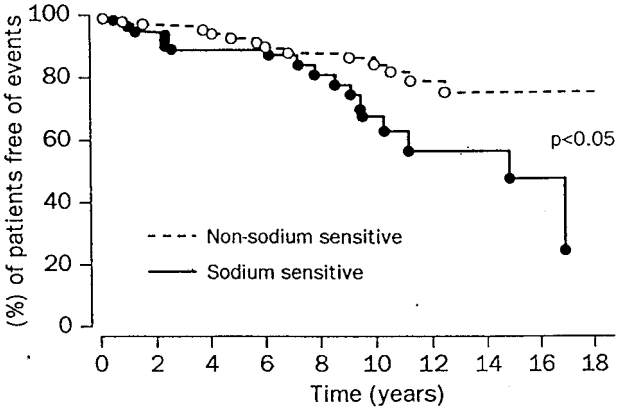

Fig 4. Kaplan–Meier plots of total cardiovascular events by sodium sensitivity in 156 hypertensive patients followed for 17 years. From reference [17].

Genetic component of salt sensitivity

Hypertension is a common but complex genetic disorder with an inheritance of about 30%. Numerous candidate genes have been implicated but a convincing link with blood pressure has been found in only a few cases [57]. In Black Americans, Svetkey *et al.* [58] have shown that salt sensitivity has also a heritable component. There is a significant familial aggregation of the blood pressure response to sodium restriction and the salt-induced changes in renal sodium handling are more closely correlated in monozygotic than in dizygotic twins [59–61]. Again, several candidate genes have been proposed, but to date, few of these proposals have been confirmed, except for the rare Mendelian forms of hypertension discussed above which produce salt-sensitive forms of hypertension. Among these candidates, polymorphisms in genes encoding for subunits of the cytoskeletal protein, adducin, have been identified in the Milan hypertensive rat strain and in humans. The presence of the polymorphism has been shown to affect kidney function through a modulation of sodium-pump activity characterized by an increased distribution of sodium pumps to the cell membrane [62,63]. Cusi *et al.* [63] have demonstrated that alpha-adducin polymorphism is associated with elevation of blood pressure in some but not all hypertensive patients. It also confers a salt-sensitivity phenotype of blood pressure in hypertensive patients and predicts their response to diuretic treatment [63]. Moreover, in patients carrying the polymorphic gene, a low plasma renin activity and an increased proximal tubular sodium reabsorption have been reported, linking this genotype to functional abnormalities of renal sodium reabsorption [64].

Salt sensitivity: a marker of renal and cardiovascular risk?

Besides its interest for the understanding of the pathophysiology of hypertension, the concept of salt sensitivity has gained increasing clinical attention because of the possible association of salt sensitivity with the risk of developing cardiovascular and renal complications. Based on experimental data, Kimura and Brenner [24] have suggested that salt sensitivity is associated with an increased intraglomerular pressure and hence a higher risk of developing glomerulosclerosis and chronic renal failure. This hypothesis has been supported by several clinical observations showing that salt-sensitive patients on a high-salt diet display an increase in filtration fraction and intraglomerular pressure which are potentially deleterious for renal function [35]. Furthermore, salt sensitivity is associated with several features known to confer a greater renal and cardiovascular risk such as microalbuminuria [65], high levels of LDL and Lp(a) [65], insulin resistance [38], a lack of nocturnal decrease in blood pressure [66], and an increased left ventricular mass [67]. Morimoto *et al.* [68] have followed a group of salt-sensitive and salt-resistant hypertensive patients for 17 years and could demonstrate that salt sensitivity is indeed an independent cardiovascular risk factor (Figure 4).

Conclusion

So far, several pathophysiological mechanisms involving alterations of renal haemodynamics and an impaired tubular regulation of sodium excretion have been proposed to explain the pathogenesis of the blood pressure response to salt. Today, evidence is growing that the renal proximal tubular handling of sodium is a key factor in the pathogenesis of salt sensitivity. More recently, many genes implicated in the renal handling of sodium have been associated with the salt sensitivity of blood pressure, but the puzzle is far from being solved. The development of new molecular techniques and possibly also new physiological tools to investigate in greater details the renal response to sodium should offer the opportunity to revisit the concept of salt sensitivity and give some new, exciting

perspectives for the explanation of the well-known, but still partly mysterious association of salt and blood pressure.

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