Altered Renal Handling of Sodium in Human Hypertension
Short Review of the Evidence

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Abstract—A pathogenic role of the kidney in hypertension has been strongly supported by experimental studies by Guyton and Dahl since the 1960s. In the early 1980s, de Wardener and MacGregor proposed that in hypertensive patients the ability of the kidneys to excrete a sodium load could be genetically impaired. Since then, “sodium-sensitive” hypertension has been the object of numerous studies, mostly on animal models because of the difficulty to investigate the renal handling of sodium in humans. More recently, considerable progress in this field has been made thanks to the in vivo study of segmental renal tubular function by the clearance of lithium and to the growing knowledge of the genetics of renal tubular sodium transport systems. The scope of this review is to briefly review the most relevant information gathered by the investigation of segmental renal tubular sodium handling in humans as related to blood pressure regulation and hypertension. In aggregate, the results of these studies strongly support the association between altered renal sodium handling and high blood pressure and suggest a causal role of genetic, nutritional, metabolic, and neurohormonal factors. All of these factors, alone or in combination, may be able to impair the normal renal tubular sodium handling and influence blood pressure homeostasis. The paradigm of the pathogenic role of the kidney in hypertension is thus relentlessly shifting toward the definition of inherited as well as acquired renal tubular defects and molecular alterations, providing a plausible explanation for the alteration in blood pressure levels. (Hypertension. 2003; 41:1000-1005.)

Key Words: sodium ▪ kidney ▪ hypertension, essential ▪ hypertension, sodium-dependent ▪ genetics

The first reports of functional renal alterations in patients with arterial hypertension were delivered in the 1940s1-2 and were followed after some time by the description of more specific alterations in the renal handling of sodium and water.3-4 Since then, hundreds of clinical and experimental studies have contributed to a better understanding of the pathogenic role of the kidney in the development and maintenance of high blood pressure. Milestones in this direction have been observations by Dahl5 and Guyton6 on the interaction between genetically determined alterations in the kidney and excess dietary sodium intake. The evidence coming from those studies led Hollenberg and Adams7 to write more than 25 years ago that “the pivotal role of the kidney in sustaining hypertension from any source or etiology (was) becoming increasingly clear.” In the early 1980s, de Wardener and MacGregor8 made a strong point by proposing that essential hypertension originates from an inherited inability of the kidney to excrete a sodium load and that its development is facilitated in a sodium-rich environment.

Over the last 2 decades, genetic studies have provided important clues about the nature of inherited functional defects in renal sodium handling that cause an increase in blood pressure. Monogenic forms of hypertension have been described that are caused by well-characterized mutations, most often associated with major alterations in the rate of renal tubular sodium chloride reabsorption9-13: All of these mutations, however, together probably account for less than 1% of the prevalence of human hypertension. The bulk of the evidence suggests that most often hypertension is the result of multiple lifestyle and metabolic and genetic interactions rather than the consequence of an isolated single gene abnormality. Several allelic variants of candidate genes for hypertension have been detected that are associated with higher blood pressure levels,14 and the number of these “susceptibility” genes is expected to grow considerably in the future. It is important to note that the large majority of these genes encode for proteins that are either directly involved with sodium transport through the renal tubular epithelia or with the endocrine/paracrine regulation of renal tubular sodium handling.12,13,15

Aside from genetic alterations, other conditions have been shown to affect the normal relationship between renal sodium handling and blood pressure. Among these, obesity stands as a major one, as suggested in the late 1980s by Rocchini and...
coworkers. These authors noted that on a low salt diet, the blood pressure of obese and lean adolescents was quite similar, but, on switching to a high salt intake, the obese group had a much greater increase in blood pressure, arguing for a reduced slope of the pressure-natriuresis relationship; this alteration reverted to normal after weight loss. Although the finding of increased salt sensitivity in obesity-associated hypertension has not been unequivocal, recent observations have focused on the prevailing influence of body fat pattern rather than absolute fat mass on the renal handling of sodium and blood pressure.

Other studies in animal models of hypertension have convincingly shown that still other metabolic and neurohormonal factors may affect blood pressure by modifying the renal handling of sodium and water, for example, the adrenergic and dopaminergic tone or endothelial dysfunction.

Investigation of Segmental Renal Tubular Sodium Handling in Humans

The study of segmental tubular sodium handling by measurement of the clearance of exogenous lithium (given in a single oral dose of 8 to 16 mmoles as lithium carbonate) has been a source of valuable information about the effects of genetic and metabolic alterations on renal tubular function and blood pressure regulation in humans. This technique is based on the principle that whereas sodium and water are reabsorbed at several sites along the nephron, the lithium ion is taken up almost exclusively at proximal tubular sites, so that the amount of substance escaping reabsorption at this level is quantitatively excreted in the urine. Because lithium is transported by the same systems driving sodium and water, an alteration in the fractional excretion of lithium argues for an alteration in the reabsorption of sodium and water at the proximal tubule. Similar considerations, though with more limitations, can be made for the clearance of uric acid, as urate transportation also occurs mainly in the proximal tubule along pathways linked to sodium and water reabsorption.

One limitation of these techniques is that they provide only indirect evidence of tubular sodium transport in vivo. Moreover, there is evidence that in extreme situations such as very low sodium intake, reduced renal perfusion pressure, or changes in ADH activity, lithium reabsorption may occur at sites beyond the proximal tubule. Nevertheless, micropuncture studies in animals have shown that under steady-state conditions, the lithium clearance provides a reasonably correct measure of the end-proximal delivery of sodium and fluid. The reliability and accuracy of this measure was tested in our laboratory under various experimental conditions. Expressing the renal clearance of lithium and uric acid as fractional excretion provides a measure that is factored for the glomerular filtration rate and of possible sources of bias such as differences in flow rate and incomplete urine collection. The measurement of glomerular filtration rate, urinary sodium excretion, and clearance of lithium allows calculation of various indexes of renal tubular sodium handling and, in particular, the fractional proximal sodium reabsorption, which is the proportion of filtered sodium that is reabsorbed at sites proximal to Henle’s loop, and the fractional distal sodium reabsorption that is the proportion of sodium escaping reabsorption in the proximal tubule that is not eliminated in the urine.

More rarely, the measurement of the clearance of “endogenous” lithium, that is, of the trace amounts of lithium naturally occurring in the bloodstream in humans, has been adopted for the study of tubular sodium handling. This technique is more expensive and time-consuming than exogenous lithium measurement and requires more sophisticated equipment not available to most laboratories. However, it provides more accurate measurements and is totally devoid of the influence that the elevated serum lithium concentrations measurable by simple atomic absorption spectrophotometry may exert per se on tubular sodium transport. The use of this tool is thus to be recommended whenever possible in future studies of renal tubular function in humans.

Renal Tubular Sodium Handling and Salt Sensitivity of Blood Pressure

Salt sensitivity of blood pressure is defined as the interindividual difference in the blood pressure response to changes in dietary sodium chloride intake; it implies an alteration in the slope of the pressure-natriuresis relationship. The measurement of lithium clearance has been used to investigate the changes occurring in segmental renal sodium handling consequent to changes in dietary sodium intake in humans, thus opening new perspectives in this area of research. A few years ago, a group of normotensive volunteers was studied on a sodium restricted diet (average, 70 mmol sodium per day) as well as on their habitual sodium-rich diet (average, 185 mmol sodium per day). On high salt intake, fractional proximal sodium reabsorption was significantly reduced in the group as a whole. However, when the subjects were classified into 3 groups according to tertiles of blood pressure response to altered sodium intake, the subjects whose blood pressure increased most on high sodium intake were the ones who had the least reduction in fractional proximal sodium reabsorption. A parallel increase in glomerular filtration rate also occurred in this group, suggesting a compensatory mechanism to counteract their inability to adequately reduce proximal sodium reabsorption and maintain a neutral sodium balance. Fractional distal sodium reabsorption on high salt intake decreased to a similar extent in all 3 groups.

More recently, a similar study has been performed in hypertensive patients with the aim to investigate the role of renal sodium handling in the blood pressure response to salt. Similar to the results of the study in normotensive subjects, significantly different trends were observed in proximal sodium reabsorption according to salt sensitivity of blood pressure: At variance with salt-resistant subjects, in whom a reduction in fractional proximal sodium reabsorption was observed on a high salt diet, the most salt-sensitive patients showed a paradoxical increase. Again, there was no difference in the response at more distal sites, nor were there any significant differences in the renal hemodynamic response to changing diet. On the basis of these findings, the authors concluded that proximal renal sodium handling is an important determinant of the alteration in the pressure-natriuresis relationship that occurs in patients with salt-sensitive hypertension, independent of changes in renal hemodynamics.
An intriguing observation from both this study and the one in normotensive subjects is the lack of compensation by more distal segments of the nephron for the alteration in the rate of proximal sodium reabsorption in the salt-sensitive subjects. A possible explanation for this finding is that the lower sodium and water load reaching the macula densa may stimulate renin (and, in turn, aldosterone) secretion and modulate the tubular-glomerular feedback mechanism to increase glomerular perfusion, as a consequence of the enhanced rate of proximal reabsorption. In the study of normotensive volunteers, a significantly higher glomerular filtration rate was indeed observed in salt-sensitive compared with salt-resistant subjects on high salt intake. Unfortunately, plasma renin and aldosterone levels were not measured.

As it is recognized that increases in arterial pressure lead to decreases in both proximal and distal tubular sodium reabsorption, the possibility that a concomitant sodium-retaining defect in the distal tubule might be masked by the higher blood pressure cannot be ruled out. Moreover, these observations in normotensive and hypertensive subjects pointing to alterations in proximal tubular sodium handling do not deny the causal role of abnormalities in distal sodium and water reabsorption in other well-characterized forms of salt-sensitive hypertension associated with reduced plasma renin activity. Examples of these are the hypertension secondary to bilateral adrenal hyperplasia or aldosterone-producing adenomas, as well as that associated with monogenic disorders such as Liddle’s syndrome or the syndrome of apparent mineralocorticoid excess.

**Genetic Bases of the Alteration in Renal Sodium Handling in Essential Hypertension**

Aside monogenic forms of hypertension, a number of relatively common genetic variants appear to be associated with higher blood pressures and increased susceptibility to hypertension; for some of them, a functional alteration has been detected. These alterations seem to account for a still very small portion of blood pressure variability in the population; nevertheless, they have provided important insights into the pathophysiological mechanisms of hypertension. In most cases, the functional alterations described are such as to affect sodium chloride transport in the kidney and are thus relevant to salt sensitivity of blood pressure. Segmental tubular sodium handling has been investigated in some cases.

The Gly460Trp variant of the α-adducin gene is associated with higher prevalence of hypertension in several populations. Another very interesting candidate gene for salt-sensitive hypertension is the one encoding for the glucagon receptor (GCGR) gene, which is associated with reduced receptor affinity for glucagon in liver cells and, in turn, with a lower secretory rate of its intracellular messenger cAMP. The Arg40Ser variant has recently been found in 3.8% of an unselected sample of Italian male adult population (n=970), only in the heterozygous condition. The carriers of this genetic variant, besides having a very high prevalence of hypertension, also had a significantly reduced fractional excretion of both lithium and uric acid (Figure 1), again suggesting an enhanced rate of proximal tubular sodium reabsorption. The mechanistic explanation for this finding is based on the notion that normally, the hepatic production of cAMP is such as to allow a significant amount of the substance to enter the systemic circulation and reach the kidney, where it affects proximal tubular function promoting sodium, phosphate, and water diuresis. In subjects carrying the Gly40Ser substitution in the glucagon receptor molecule, an impaired hepatic cAMP production occurs. In turn, the cAMP concentration in the blood is expected to be reduced, and so will its influence on renal proximal sodium transport, with resultant defective natriuresis and a modification of the pressure-natriuresis relationship.

The dopaminergic system has been suggested to play an important role in the regulation of renal sodium and water handling and in maintaining fluid and electrolyte balance. Genetic-based variation in the function of this control system is thus likely to influence susceptibility to hypertension. Very recently, single nucleotide polymorphisms of a G protein-coupled receptor kinase, GRK4-γ, have been associated with increased activity of this enzyme: The resulting increase in receptor phosphorylation results in the uncoupling of the dopamine-1 receptor from its G protein/effector enzyme complex in renal proximal tubular cells. The same study showed that arterial hypertension develops in transgenic mice expressing the polymorphic variant. There is no information at present about the frequency of GRK4-γ polymorphism in the population, nor has an investigation of renal tubular sodium handling been carried out in affected subjects.

Another very interesting candidate gene for salt-sensitive hypertension is the one encoding for the serum and glucocorticoid-regulated kinase, SGK1. SGK1 stimulates the expression of epithelial Na+ channels on binding of aldosterone to its own receptor, thus promoting sodium chloride reabsorption. Two polymorphic variants of the SGK1 gene have been reported to be associated with higher blood pressures. On the other hand, SGK1-knockout mice appear to have an impaired ability to decrease urinary sodium...
excretion on dietary sodium chloride restriction and display a tendency to lower blood pressure. Also in this case, the investigation of renal tubular sodium handling in individuals carrying the different allelic variants are warranted.

The fundamental role of renal tubular sodium handling in blood pressure regulation is further supported by the description of genetic mutations that impair tubular sodium and water reabsorption and cause a tendency to chronically lose sodium. The paradigm of these conditions is represented by Gitelman’s syndrome, which is caused by loss-of-function mutations in the gene encoding for a sodium chloride cotransporter at the distal convoluted tubule: The associated alteration in electrolyte transport results in a reduced rate of sodium reabsorption and salt wasting. Individuals homozygous for the defective allele have a significantly lower blood pressure and an increased appetite for salt that leads them to consume a very high sodium diet.

Thus, whereas genetic mutations leading to an increased rate of renal sodium reabsorption tend to elevate blood pressure, the opposite also occurs; in aggregate, these findings consistently support the importance of salt balance in determining susceptibility to hypertension in humans.

Metabolic and Neurohormonal Abnormalities Associated With Altered Tubular Sodium Handling and High Blood Pressure

Several studies in humans as well as in dogs suggested that obesity is frequently associated with an altered pressure-natriuresis relationship and possibly with increased salt sensitivity of blood pressure. The segmental tubular sodium handling was recently investigated in relation to body mass and body fat pattern in untreated male participants of the Olivetti Heart Study. Using body mass index as an indicator of total fat mass, waist circumference as a measure of abdominal adiposity, and arm circumference as an index of peripheral fat, it was found that for increasing values of body mass index and waist circumference the rate of fractional proximal sodium reabsorption also increased. This relationship was statistically significant, accounting for age and for blood pressure. On the other hand, the relation between proximal renal sodium handling and arm circumference was flat, suggesting that abdominal adiposity is specifically associated with an alteration in proximal tubular sodium reabsorption. In the same study, a direct comparison of fractional proximal sodium reabsorption in normal weight men versus overweight men showed that overweight men with greater abdominal fat deposition had an increased rate of proximal sodium reabsorption (Figure 2), and this was associated with hyperinsulinemia, insulin resistance, and higher blood pressure.

Several mechanisms may be responsible for the enhanced tubular sodium reabsorption in relation to central adiposity. Tubular sodium reabsorption depends on the activity of ion transport systems, which are modulated by neural, endocrine, paracrine, and physical factors. One important such factor is insulin, which has an acute antinatriuretic effect also apparent in obese individuals despite concomitant resistance to the other metabolic effects of the hormone. The sodium-retaining effect of acute hyperinsulinemia is probably exerted at a site beyond the proximal tubule, but chronic hyperinsulinemia (and/or insulin resistance) might also affect proximal sodium reabsorption by inhibiting glucagon-stimulated hepatic cAMP production and thus impairing the cAMP natriuretic influence.

Another important factor might be an increase in renal sympathetic tone. Evidence of enhanced sympathetic tone in obesity has been found in many but not all studies in humans. This clinical observation is matched by the results of experimental studies showing that obesity induced by high-fat, high-calorie intake in the dog is associated with sympathetic activation and an NaCl-dependent form of hypertension, attenuated by concomitant administration of clonidine. Kassab et al studied the role of this increased adrenergic tone at the renal level by investigating the effects of renal denervation on sodium balance and blood pressure in mongrel dogs made obese by high fat intake. When a group of dogs submitted to renal denervation and a control group of sham-operated dogs were given a high fat diet for 5 weeks, body weight increased to a similar extent in both groups, as did heart rate, denoting a similar degree of systemic sympathetic activation; however, blood pressure did not increase in the renal denervated animals, at variance with the control group. Noteworthy, the difference in blood pressure was paralleled by a difference in cumulative sodium balance: Whereas in the control group a positive sodium balance developed together with the increase in weight and blood pressure, the degree of sodium retention observed in the renal denervated dogs was much smaller, suggesting an important role for sympathetic activation in promoting the sodium retention associated with development of obesity.

Finally, a possible role for alterations in intrarenal physical forces in the enhanced tubular sodium and water reabsorption observed in obesity is supported by evidence from animal experimental studies: Whether this also occurs in humans with abdominal adiposity is unknown.

Whatever the mechanisms for the altered renal tubular sodium handling observed in obese individuals, it may be expected that the unfavorable consequences of this alteration in renal sodium handling will be fully expressed in the presence of a high habitual dietary salt intake.

Conclusions

Increasing evidence from clinical and experimental studies supports the contention that altered renal sodium handling has
a major pathogenic role in hypertension. An altered tubular sodium handling has been associated with several genetic mutations and with polymorphic variation in a growing number of genes interacting with each other and with various metabolic, nutritional, and neurohormonal factors, among which is a high salt intake. The elucidation of the precise role of the gene products involved in this process is a key objective for a better understanding of the molecular bases of high blood pressure.

The investigation of segmental renal tubular sodium handling in humans, despite its inherent methodological limitations, has substantially contributed to our present understanding of pathogenetic mechanisms of hypertension. Further progress is to be expected if greater attention is paid to this intermediate phenotype and if the measurement of “endogenous” lithium clearance is preferentially adopted for its quantitative evaluation.

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