SEMINARS IN
NEPHROLOGY

Channels, Carriers, and Pumps in the Pathogenesis of Sodium-Sensitive Hypertension

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Sodium-sensitive hypertension is thought to be dependent on primary alterations in renal tubular sodium reabsorption. The major apical plasma membrane Na^+ transporters include the proximal tubular Na^+-H^+ exchanger, the thick ascending limb Na^+-K^+-$2Cl^-$ cotransport system, the distal tubular Na^+-Cl^- cotransporter, and the collecting duct epithelial sodium channel (ENaC). This article explores the role of each transporter in the pathogenesis of hypertension. Although the contribution of the proximal tubule Na^+-H^+ exchanger is not yet defined completely, more convincing data have been generated about the importance of the Na^+-K^+-$2Cl^-$. Indeed at least 2 forms of hypertension appear to be related to the up-regulation of the transporter: the so-called *programmed hypertension* induced by low-protein diet during pregnancy and the early phase of hypertension in the Milan strain of rats. With respect to the Na^+-Cl^- cotransporter this may be overactive caused by inactivating mutation of WNK4 as in the Gordon syndrome, although it is the main actor for the maintenance phase of the hypertension found in the Milan strain of rats. Finally, the contribution of the ENaC has been established clearly; indeed, in the Liddle syndrome the mutation of the ENaC gene leads to a longer retention of the channel on the cell surface of collecting duct principal cells, thus inducing stronger sodium reabsorption along this segment. All these examples clearly indicate that renal sodium transporters may be responsible for various types of sodium-sensitive hypertension.
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Hypertension is the most frequent disorder of the human population. Both genetic and nongenetic factors are involved and high salt intake has been proposed as a major risk factor. Because sodium metabolism largely is dependent on the kidney, it is obvious that this organ may play an important role in the pathogenesis of hypertension. The concept that the kidney participates in long-term control of arterial pressure has been proposed by Guyton et al,[1] who were the first to recognize that because an increase of arterial pressure directly increases sodium excretion, hypertension can develop only when the pressure natriuretic relationship is impaired. Subsequent renal transplantation studies strongly have supported this hypothesis and indicate that some form of dysfunction in renal sodium reabsorption underlies the development of hypertension in human beings and experimental animals.[2] Finally, recent human genetic studies have shown that mutations of genes, encoding for proteins expressed in the kidney and involved in tubular ion transport, are associated with modifications of systemic blood pressure. For instance, loss of function mutations of transport molecules in the thick ascending limb of Henle's loop leads to Bartter's syndrome, and defective thiazide-sensitive Na^+-Cl^- cotransporter, present in the distal tubule, is the cause of Gitelman's syndrome.[3] The modifications of these ion-transporting systems are characterized by urinary sodium loss resulting in orthostatic hypotension. In contrast, gain-of-function mutations of amiloride-sensitive sodium channels in the collecting ducts generate Liddle's syndrome, which phenotypically is characterized by systemic hypertension.[4] In kidney epithelia, sodium reabsorption proceeds via sodium carriers, channels, and pumps. In addition to the Na^+-K^-, adenosine triphosphatase (ATPase), and the ubiquitous sodium pump, which at the level of tubular cells is localized

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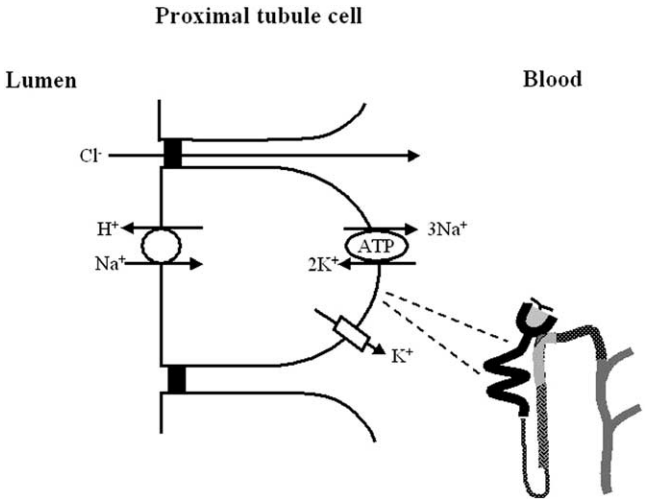

Figure 1 Proximal tubular cell showing the Na^+-H^+ exchanger as the main sodium transporter localized on the apical membrane.

exclusively on the basal lateral membrane, there are various luminal transporters that control the entry of sodium from the lumen into the tubular cells. It now almost is certain that, in the regulation of transepithelial sodium transport, the rate-limiting step is not localized at the exit site (ie, on the basal lateral membrane through the Na^+-K^--ATPase) but on the entry step. Cloning of these transporters has led to the development of complementary DNA probes and antibodies that now are being used for studies on the regulation of renal tubule sodium transport.[5] Thus far, the most important luminal transporters are as follows: the type 3 sodium-hydrogen exchanger (NHE3) at the level of the proximal tubule,[6] the bumetanide-sensitive sodium-potassium- 2 chloride cotransporter (NKCC2) along the thick ascending limb of Henle's loop (TAL),[7] the thiazide-sensitive sodium-chloride cotransporter (NCC) in the distal tubule,[8] and the amiloride-sensitive sodium channel (ENaC) in the distal tubule and in the collecting duct.[9] The assessment of the role of each transporter is presumed to contribute largely to our knowledge of the pathogenesis of sodium-dependent hypertension.

Na^+-H^+ Exchanger Family

NHEs extrude protons from and take up sodium ions into cells. The secreted H^+ are used to reclaim the filtered bicarbonate and therefore the Na^+-H^+ exchanger is the most important transporter involved in maintaining systemic acid-base balance. However, because the exchanger not only secretes H^+ but also absorbs Na^+ ions, it is involved directly and indirectly in the reclamation of sodium. Indeed, the absorption of $NaHCO_3^-$ drives the absorption of water and increases luminal chloride concentration. The transepithelial chloride gradient in turn creates a lumen-positive transepithelial voltage difference that drives paracellular sodium reabsorption. Therefore, the Na^+-H^+ exchanger in the apical membrane of proximal tubule cells contributes to transcellular and paracellular absorption of Na^+, Cl^-, HCO_3^-, and water (Fig 1). Murer et al[10] were the first to show the electroneutral exchange of Na^+ against H^+ in brush-border membrane vesicles isolated from kidney cortex. Since then, numerous studies have been performed to characterize the Na^+-H^+ exchanger that today is known as NHE-3 and it is part of a large family composed of 8 cloned isoforms.[11] An increase or decrease of plasmalemma NHE-3 expression not only is an integral part of homeostatic compensation in conditions of chronic metabolic acidosis or alkalosis and chronic dietary sodium depletion, but also is associated with several pathophysiologic states of renal disorders. A central role of NHE-3 in the genesis of essential hypertension is suggested by observations that spontaneously hypertensive rats (SHR) exhibit increased expression and activity of NHE-3 in the proximal tubule.[12] Internalization and inactivation of plasma membrane NHE-3, on the other hand, seems to be in charge for the blunted natriuretic effect seen during acute or sustained hypertension in kidney from spontaneously hypertensive animals or human beings.[13] A decreased sensitivity of NHE-3 to dopamine may play an important pathophysiologic role. Despite similar levels of DA1 receptors and Gs proteins, dopamine and DA1-receptor antagonists inhibited the Na^+/H^+ exchanger in brush-border membrane vesicles isolated from SHR kidneys less efficiently than the antiporter from control rats. It seems that the coupling between the DA1 receptors and Gs proteins was attenuated in SHR causing a less depressed (ie, higher) activity of NHE-3.[14]

Evidence that blood pressure can be altered by alterations in renal tubule Na^+-H^+ antiporter activity also comes from recent molecular biology studies. The NHE-3 knockout mouse exhibits mild hypotension compared with the wild-type mouse.[15] Finally, in a systematic analysis of Na^+-H^+ exchanger activity and NHE-3 expression performed in renal cortical tubules from SHR and Wistar-Kyoto rats before and during the development of hypertension, LaPointe et al[16] reported that Na^+-H^+ antiporter activity and NHE-3 abundance are increased in tubules from prehypertensive SHR and that they remain increased in the SHR after the development of mild or severe hypertension as compared with age-matched normotensive Wistar-Kyoto rats. These data show that NHE-3 protein and activity along the renal proximal tubules from SHR antedates the development of hypertension and may contribute to its initiation. Moreover, they show why the reabsorptive capacity for sodium and fluid in proximal tubules (ie, inappropriate increase in NHE-3 protein expression) from SHR is not suppressed despite the development of severe hypertension.

Experimental evidence suggests that increased proximal NHE-3 activity also may contribute to the development of hypertension in uncontrolled diabetes mellitus. In rats the generation of diabetes mellitus causes an increase in renal brush-border membrane Na^+-H^+ exchanger activity.[17] These findings were confirmed further by the remark that high levels in glucose concentration increased NHE-3 activity and NHE-3 abundance in the plasma membrane of the opossum kidney cell line. Importantly, increased NHE-3 activity continued after the removal of cells from the hyperglycemic media.[18] Based on these results, it was postulated that NHE-3 may be responsible for renal NaCl retention and associated

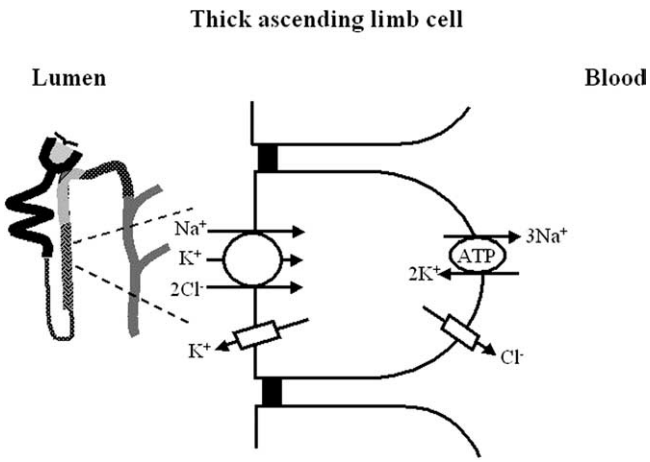

Figure 2 Major ion transporters and channels present in the thick ascending limb cell.

expanded extracellular fluid volume, which then may cause hypertension and diabetic nephropathy.

Na^+-K^+-$2Cl^-$ Cotransporter

The TAL reabsorbs 20% of the glomerular ultrafiltrate, regulates divalent mineral excretion, and plays a key role in the production and maintenance of renal medullary tonicity. The major pathway for sodium reabsorption along the TAL is NKCC2, the main pharmacologic target of loop diuretics (Fig 2). Up-regulation of NKCC2 has been reported in the early phase of prenatally programmed hypertension induced by a maternal low-protein diet during pregnancy.[19] The fact that the prenatal environment can modify the adult blood pressure profile is supported by both epidemiologic and experimental studies.[20,21] These studies show that the target of the programming is renal sodium handling by the fetus and they are consistent with the hypothesis that the pathogenesis of sustained hypertension involves the kidneys because a normal renal pressure-natriuresis response would correct the hypertension. It also is possible that the fault lies in the reduced final number of nephrons, which limits filtration of sodium and leads to expansion of extracellular fluid volume as proposed by Brenner and Chertow.[22]

The strong stimulation of the Na^+-K^+-$2Cl^-$ cotransporter potentially could contribute to the significant increase in blood pressure. Several lines of evidence support this hypothesis. First, the thick ascending limb is an important site of sodium transport; roughly 20% of the filtered sodium load normally is reabsorbed at this level. Second, apical sodium entry in the TAL is mediated mainly by the bumetanide-sensitive Na^+-K^+-$2Cl^-$ cotransporter[23] as shown by the copious natriuresis associated with the use of loop diuretics, an effect that it is enhanced by their inhibiting action on tubuloglomerular feedback.[24] Third, patients carrying a mutation with a loss of function of the NKCC2 gene (type I Bartter's syndrome) are characterized by orthostatic hypotension.[25] Finally, mice lacking the NKCC2 gene suffer from severe salt wasting, resulting in rapid death.[26]

At the TAL level, sodium reabsorption is coupled to potassium recycling through the luminal membranes by renal outer medulla potassium channels (ROMK)[27] and to chloride exit through the basal lateral membrane by specific chloride channels.[28] The activity of ROMK channels is critical to the sodium reabsorption along the TAL because these channels recycle potassium to the tubule lumen, which is necessary to maintain a sufficient luminal concentration of potassium, a prerequisite to reabsorb sodium via the cotransporter.[23] The recycling of potassium through the ROMK channels is also the primary determinant of the lumen-positive transepithelial potential that drives passive reabsorption of sodium in the TAL via the paracellular pathway. Thus, the reported increased expression of NKCC2, coupled with up-regulation of ROMK, would be expected to enhance both active and passive sodium chloride transport. This hypothesis is consistent with recent findings showing that in Dahl salt-sensitive rat kidneys there is increased NKCC2 and ROMK expression[29] and with the observation that in the TAL of the same rats the chloride reabsorption and the lumen-positive transepithelial potential are increased.[30] With respect to chloride transport the available data indicate that the TAL reabsorbs about 30% of the chloride that is filtered at the glomerulus and thereby plays an important role in the maintenance of body salt and fluid balance. The model includes a chloride luminal uptake by the NKCC2 with potassium recycling over the apical membrane by ROMK, an intracellular accumulation, and, finally, an exit step at the basal lateral membrane via the specific ClC-Kb channels. This model puts the ClC-Kb channels with the apical NKCC2 cotransporter and ROMK potassium channels into a functional relationship. This interaction is supported strongly by the genetic findings that mutations with loss of function of either NKCC2 or ROMK or ClC-Kb are associated with Bartter's syndrome,[31] an autosomal-recessive salt-wasting disorder characterized by reduced sodium chloride reabsorption in the TAL.[32] Recently, it was shown that ClC-Kb channels have a β subunit, named *Barttin*, that is crucial for chloride reabsorption along the TAL;[33] its functional inactivation results in renal salt wasting, causing Bartter's syndrome type IV.[34] However, at the present time there are no reports about the involvement of the TAL chloride channel in the pathogenesis of hypertension.

Na^+-Cl^- Cotransporter

The distal convoluted tubule reabsorbs up to 7% of the glomerular filtrate; along this segment the major sodium reabsorption pathway in the apical membrane is the NCC, which is the major target for thiazide diuretics (Fig 3).[35] The likelihood that NCC may be involved in the pathogenesis of genetic hypertension has been forwarded by Beaumont et al[36] who found that the thiazide receptors in the renal cortex in SHR increased with age together with the development of hypertension. Evidence for a potential inference of the thiazide receptor in the pathogenesis of hypertension also has been gained by studies performed on Dahl salt-sensitive rats, in which the expected down-regulation in thiazide receptors, when rats were switched from low- to high-salt diets, did not

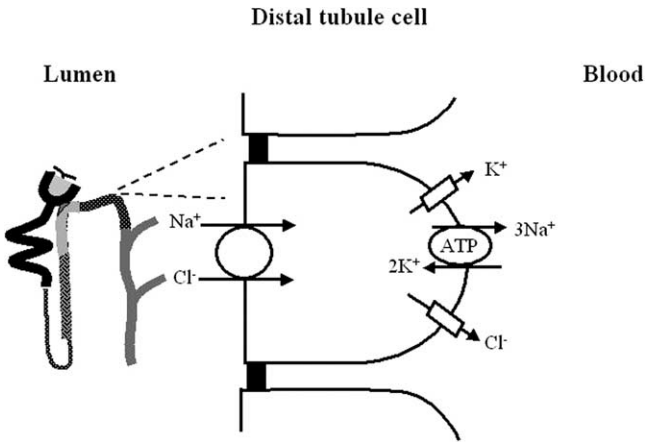

Figure 3 Na^+-Cl^- cotransporter is the major entry pathway for sodium in the distal tubule cells.

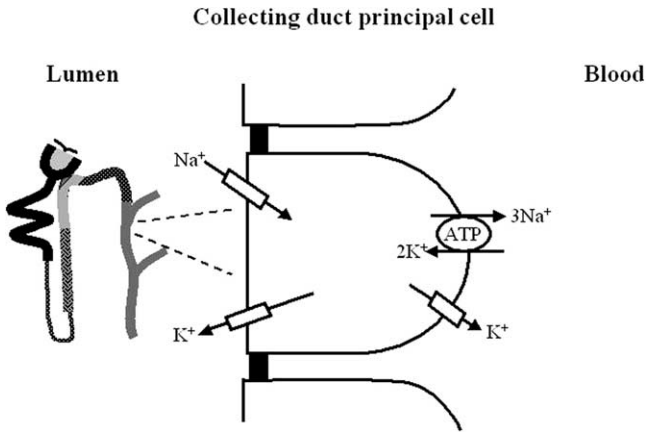

Figure 4 Along the collecting duct cell the sodium conductance localized on the apical membrane is the major route for sodium entry into the cell.

happen.[37] However, Moreno et al[38] recently showed that NCC transcript levels did not change in 3 models of experimental hypertension (including SHR). Therefore, to explain the reported increase in thiazide-receptor density, other NCC functions must be envisaged such as stability, protein translation rate, and intracellular distribution.

The possibility that NCC may be responsible for some forms of hypertension has been supported recently by genetic studies performed in patients affected by Gordon syndrome. These patients suffer from hypertension that is associated with chloride-dependent sodium retention, accompanied by increased serum potassium levels and acidosis; therefore, clinically, this is the opposite of Gitelman syndrome.[39] Despite the clinical indication of overactivity of NCC, linkage to this gene was excluded formally in favor of at least 3 other loci.[40-42] Two responsible genes now have been identified encoding 2 members of a novel serine/threonine kinase family named *WNK* (with no lysine K, ie, lacking a lysine typical of the catalytic domain of this kinase family): WNK1 and WNK4.[43] WNK1 is expressed ubiquitously in many tissues and is associated particularly with chloride-transporting epithelia; in the kidney, WNK1 is localized to the aldosterone-sensitive distal nephron. WNK4 expression has a highly restricted expression profile: the protein is detected only along the distal nephron of the kidney. Of particular interest is the recent evidence that WNK4 acts as a negative regulator of NCC function.[44,45] Disease-causing mutations relieve this inhibition, leading to NCC overactivity and therefore to sodium-dependent hypertension.

Sodium Channels

In the kidney the ultimate regulation of sodium reabsorption occurs in the collecting duct via a process of conductive transport mediated by the ENaC. This channel is located on the apical membrane of collecting duct principal cells and represents the rate-limiting step in sodium reabsorption in this segment[46] (Fig 4). Abnormalities of function of this channel have been shown to be important in the pathogenesis of hypertension seen in patients with Liddle's syndrome.[4] This observation may point to a significant impact of sodium channel dysregulation in volume-overload states such as sodium-sensitive hypertension.

The ENaC is characterized by its remarkable ion cationic selectivity, gating kinetics characterized by long closing and opening times and a high sensitivity to amiloride. ENaC is a heteromultimeric channel, composed of 3 homologous α, β, and γ subunits.[47] Co-expression of all 3 subunits in the *Xenopus oocyte* constitutes the channel with all the physiologic and pharmacologic properties of the native channel. Similar experiments show that the α-subunit is essential for the function of the channel, but the channel activity is enhanced by association with β and γ subunits,[48] a finding that has been confirmed by the generation of gene knockout mice for the individual subunits.[49] Finally, aldosterone and vasopressin regulate ENaC-dependent sodium reabsorption by changing the expression of the individual ENaC subunits.[50,51] It has been shown that α-ENaC is present mostly at the apical domains of the principal cells, whereas β and γ-ENaC are localized mainly in cytosolic vesicles.[52] The significance of this different subcellular distribution of the 3 subunits has not been ascertained.

As discussed earlier, the role of ENaC in the pathogenesis of hypertension has been reinforced by the molecular genetic studies on patients affected by Liddle's syndrome. This is an autosomal-dominant form of salt-sensitive hypertension characterized by early onset of severe hypertension, hypokalemia, metabolic alkalosis, and low renin and aldosterone secretion.[4] The syndrome results from specific mutations in the proline-rich domain of either the β or γ subunits of ENaC (PPXY motif), which prevents the binding of the physiologic repressor Nedd4-2 that normally promotes the endocytic retrieval of the channel.[53] As a consequence of this mutation ENaC is retained on the cell surface of collecting duct principal cells. Recently, a mouse model for Liddle syndrome was generated.[54] Under high salt intake the Liddle mice develop hypertension, metabolic alkalosis, and hypokalemia, thus replicating most of the symptoms of the human patients affected by Liddle's syndrome and confirming that the specific

gene expressed in the kidney may be responsible for a particular form of salt-sensitive hypertension.

Sodium Transporters in the Milan Hypertensive Rats

An useful model to study hypertension is the Milan hypertensive strain of rats; it has been shown clearly that these animals develop hypertension because of a primary alteration in renal tubular sodium reabsorption.[55] It also has been shown that induction of hypertension is preceded by a phase of salt retention caused by increased tubular sodium reabsorption.[56] Subsequent experiments have also clarified that the primary event explaining the enhanced tubular sodium reabsorption is the increased activity and expression of Na^+-K^+-ATPase.[57] Recent studies performed by our group have indicated clearly that 2 important luminal sodium carriers, expressed in distinct nephron segments, are involved in the pathogenesis of hypertension in this rat model: the NKCC2, localized along the TAL, is up-regulated during the induction of hypertension (young Milan rats),[58] whereas the NCC, expressed in the distal tubule, is increased significantly both at messenger RNA and protein levels during the maintenance phase of hypertension (old Milan rats).[59]

With respect to ENaC in young Milan normotensive strain of rats (MNS) there is a modest, although significant, down-regulation of the α-ENaC. Because apical Na^+ entry is believed to constitute the rate-limiting step in Na^+ reabsorption in the different nephron segments, it is likely that decreased expression of apical membrane sodium carriers reflects inhibition of transepithelial Na^+ transport. Therefore, it is obvious to postulate that in this model of sodium-dependent hypertension, the early phase is characterized by a decreased Na^+ transport in the tubular segments beyond the TAL. Such a phenomenon is not unique to this model because in the prenatally programmed hypertension the vigorous up-regulation of NKCC2 is compensated partially by a slight reduction of α-ENaC.[19] With respect to the β and γ subunits, the lack of change is not surprising because in other experimental models associated with changes in renal sodium handling the regulation of the channel may be dependent from other factors such as a degradation of the γ subunit.[60]

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