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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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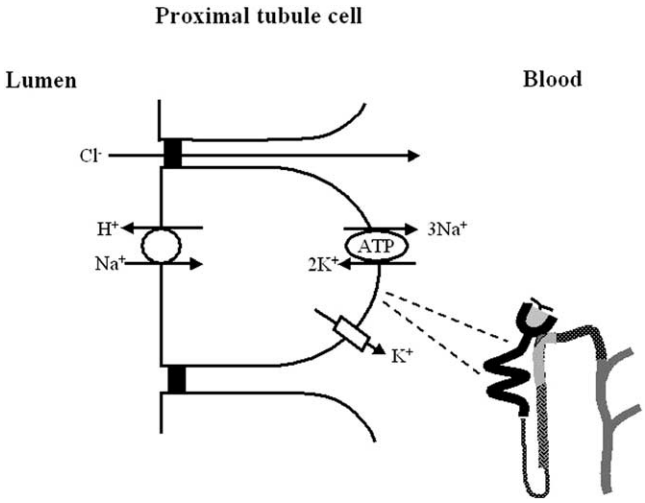

Figure 1 Proximal tubular cell showing the Na^+-H^+ exchanger as the main sodium transporter localized on the apical membrane.

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