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Intrarenal Transport and Vasoactive Substances in Hypertension

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Abstract—Blood pressure is influenced by several vasoactive factors that also regulate nephron transport. An imbalance in regulation of salt reabsorption by the nephron contributes to hypertension. In the spontaneously hypertensive rat (SHR), the responses to dopamine and angiotensin II in the proximal nephron are diminished and enhanced, respectively. This partially explains why the proximal tubule of SHR absorbs more salt and water than that of normotensive controls. In the Dahl salt-sensitive rat, defects in NO signaling and alterations in the arachidonic acid/cytochrome P450 pathways are associated with increased salt reabsorption by the thick ascending limb. In other animal models, such as the deoxycorticosterone acetate (DOCA)–salt rat, hypertension develops as the result of an induced hormonal imbalance. By mimicking the effects of aldosterone, DOCA stimulates sodium reabsorption in the collecting ducts, causing salt and fluid retention. Thus, this model is similar to inherited forms of human hypertension caused by abnormal regulation of transport by mineralocorticoids, such as apparent mineralocorticoid excess and glucocorticoid-remediable aldosteronism. Overall, these findings demonstrate the significance of vasoactive compounds in regulating nephron transport and controlling blood pressure. However, important questions regarding humoral control of nephron transport and its implications in hypertension remain unanswered, and intensive research in these areas is required. (*Hypertension*. 2001;38[part 2]:621-624.)

Key Words: renal circulation ■ water-electrolyte balance ■ kidney ■ rats, Dahl ■ rats, inbred SHR ■ deoxycorticosterone

Renal solute and water reabsorption is closely regulated to maintain electrolyte homeostasis and extracellular fluid volume. An appropriate balance between fluid intake and renal excretion is required for long-term regulation of blood pressure.¹ When body fluid homeostasis is challenged, several humoral factors capable of modifying salt and water reabsorption are released, thereby maintaining fluid balance. Many of these factors are also potent vasoactive substances that affect peripheral resistance and exert synergistic effects on tubular reabsorption. It would be impossible to describe the blood pressure effects of every vasoactive substance that regulates intrarenal transport within this short review. Therefore, we will focus on evidence that correlates abnormalities in intrarenal tubular transport with changes in blood pressure in 3 well-known experimental models of hypertension.

Animal Models of Hypertension and Intrarenal Transport

Various animal models have been created to study the complex mechanisms involved in the development of hypertension. These models vary widely with regards to their ability to simulate human hypertension. Genetic models of hypertension such as the spontaneously hypertensive rat (SHR) and the Dahl salt-sensitive (DS) rat are suitable for

studying the factors involved in the development of human inherited and salt-sensitive hypertension. Animal models in which a humoral-hormonal imbalance is generated, such as deoxycorticosterone acetate (DOCA)–salt hypertension, are suitable for the study of factors involved in secondary forms of hypertension. We will investigate the role of vasoactive factors and nephron transport in these 3 animal models.

Spontaneously Hypertensive Rats

The SHR is a genetic animal model of hypertension created by selective inbreeding of Wistar-Kyoto rats (WKY). SHR develop hypertension and end-organ damage spontaneously without further treatments such as salt loading. This model of hypertension is categorized as a “normal renin” model because renin is within the normal range. However, it is clear that the renin levels of SHR are high in light of the hypertension. Although SHR show normal renin levels, angiotensin II plays an important role in the development of hypertension in this model. This is evidenced by studies showing that treatment of young SHR with either ACE inhibitors or angiotensin II type 1 (AT₁) receptor antagonists prevents the development of hypertension, and these antihypertensive effects persist even after cessation of treatment.²

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Renal transplant studies between SHR and WKY have shown that hypertension follows the path of the kidney; ie, if an SHR kidney is placed in a WKY, the animal will become hypertensive. If the reverse is done, the blood pressure of SHR will decrease.^{3,4} Several alterations in kidney transport have been associated with the development of hypertension in SHR. Exaggerated salt and water retention occurs in young SHR because of reduced glomerular filtration rate (GFR) and both total and fractional urinary sodium excretion.⁵ The decrease in fractional sodium excretion has been postulated to be caused by abnormalities in several transport mechanisms, primarily in the proximal tubule.

In the proximal tubule, sodium is absorbed via apical transporters, including the Na^+/H^+ exchanger, which is responsible for bicarbonate absorption, and the sodium/glucose, sodium/amino acid, and sodium/phosphate co-transporters. Quantitatively the Na^+/H^+ exchanger accounts for the bulk of sodium absorbed in this segment. The electrochemical gradient driving sodium entry is provided by basolateral Na^+,K^+ -ATPase, which extrudes sodium into the extracellular space.

Isolated, perfused tubule preparations and micropuncture experiments have shown that proximal tubules of young prehypertensive SHR reabsorb more sodium than do WKY.⁶⁻⁸ However, the reason for this remains unclear. Dramatic increases in Na^+/H^+ exchange activity have been reported in young SHR proximal tubule cells, without a change in transporter mRNA abundance and only a modest increase in protein abundance.⁹ These results suggest that increased Na^+/H^+ exchange activity is due to altered regulation. In fact, it has been reported that fluid absorption in the proximal tubule in response to angiotensin II is higher in SHR than in WKY, possibly because of an increased number of AT_1 receptors.^{6,10} This increase in fluid absorption is likely due to enhanced Na^+/H^+ exchange. Angiotensin stimulates Na^+/H^+ exchange to a greater extent in SHR proximal tubules than in those of WKY.¹¹ These data are consistent with *in vivo* data showing that blockade of the renin-angiotensin system prevents the development of hypertension in this model.

Net sodium transport can be enhanced by increasing either sodium entry or exit. Proximal tubules of SHR have increased Na^+,K^+ -ATPase activity compared with those of WKY.¹² However, recent reports describe a decrease in mRNA for the α - and γ -subunits of Na^+,K^+ -ATPase in SHR compared with age-matched WKY.^{13,14} These studies suggest that the increase in sodium pump activity is not caused by increased protein expression, but rather by altered regulation. In fact, the response of proximal tubule Na^+,K^+ -ATPase activity to various hormones is altered in SHR.

The proximal nephron produces dopamine, which acts as an autacoid decreasing Na^+,K^+ -ATPase activity.^{15,16} Intrarenal infusion of dopamine agonists increases natriuresis less in SHR than in WKY.¹⁷ This defect is in part because dopamine inhibits proximal nephron Na^+,K^+ -ATPase less in SHR than in WKY.¹⁸ The exact molecular mechanism responsible for the decreased response to dopamine is not fully understood. However, it may involve defective coupling of the dopamine D_1 receptor with adenylate cyclase,¹⁹ as defective G protein signaling has been linked to the failure of dopamine to inhibit Na^+,K^+ -ATPase.²⁰ These data suggest that the inability of endogenous dopamine to inhibit Na^+,K^+ -ATPase could increase transport rates as observed in the proximal tubule of SHR.

In summary, multiple signaling events leading to increased fluid and sodium reabsorption by the proximal tubule appear to be altered in SHR, especially during the development of hypertension. These same defects may also account for the altered vascular responses observed in this model. Although we are beginning to understand differences in proximal tubule transport and how they are regulated in SHR and WKY, we know little about such processes in other nephron segments. Clearly, this is an area where more work needs to be done.

Dahl Salt-Sensitive Rats

DS and Dahl salt-resistant (DR) rats were developed from the normotensive Sprague-Dawley strain. In this model, both genetic and environmental factors are involved in the development of hypertension. When DR and DS rats are placed on a high-salt diet, DS will become hypertensive whereas DR will remain normotensive. Several organ systems—including the cardiovascular, nervous, and renal as well as humoral and endocrine systems—are involved in hypertension in the DS rat. However, the renal system appears to be predominant among these. Similar to transplant experiments in SHR, replacing a kidney of a DR rat with a kidney from a DS donor induces hypertension in the DR rat. Conversely, replacing a DS kidney with a DR kidney lowers blood pressure in the DS rat.^{21,22} The characteristics of hypertension in the DS rat are similar in nature to those observed in African Americans. These include rapid onset of hypertension, salt sensitivity, and low plasma renin activity. Similar to the DS model, there is also a high prevalence of end-stage renal disease and end-organ damage in hypertensive blacks.^{23,24}

Several explanations for the transplant data have been offered, including reduced pressure natriuresis and inappropriate salt absorption along the nephron. In fact, the reduced pressure natriuresis in the DS rats may be the result of defects in nephron transport. *In vivo* micropuncture experiments showed that DS rats exhibited higher chloride absorption rates in the loop of Henle than did normotensive DR rats.^{25,26} However, the exact nephron segment responsible was not identified. Using isolated perfused tubules, we²⁷ and others²⁸ have shown that DS rats have a higher rate of chloride absorption in the thick ascending limb (THAL) than DR rats.

Recent studies provide evidence suggesting that defects in at least 2 different signaling mechanisms account for enhanced THAL transport in DS rats, ie, the NO and the arachidonic acid/cytochrome P450 pathways. Consistent with its known natriuretic and diuretic effects, NO inhibits transport in various nephron segments, including the THAL. NO is produced by the enzyme NO synthase (NOS), which uses the amino acid L-arginine as substrate. Involvement of NO in the development of hypertension in DS rats is supported by data showing that systemic or intrarenal infusion of L-arginine prevents hypertension and also restores the pressure-natriuresis relationship in DS rats.^{29,30} These results suggest that a defect in either NO synthesis or the response to NO is the cause of salt sensitivity in DS rats. We found that in normal Sprague-Dawley rats, NO inhibits THAL NaCl absorption.³¹ When we studied DS rats, we found that the inhibitory effect of low concentrations of NO donors on NaCl transport was blunted in DS compared with DR rats.²⁷

However, there was no difference when high concentrations were used. This suggests that the response to NO is diminished but does not rule out the possibility that NO production is also reduced.

Because the effects of NO in the THAL are mediated by activation of soluble guanylate cyclase and hence an increase in cGMP, we studied the ability of NO to stimulate cGMP production in DS and DR rats. We found no difference in NO-stimulated cGMP production in DS compared with DR rats, suggesting that the defect in the response to NO occurs downstream from cGMP production.²⁷

Another signaling system, the arachidonic acid/cytochrome P450 pathway, has also been associated with the pathogenesis of hypertension in the DS rat. In this pathway, arachidonic acid is metabolized to HETEs and epoxyeicosatrienoic acids (EETs) by cytochrome P450 monooxygenases. The THAL produces 20-HETE, which inhibits NaCl transport by the THAL. Abnormalities in renal P-450 metabolism resulting in decreased 20-HETE production have been found in DS rats.³² These animals express lower levels of cytochrome P450 monooxygenase in the renal outer medulla, and its alleles cosegregate with blood pressure.³³ Finally, in isolated perfused THALs from DS rats, a deficiency in 20-HETE production has been shown to contribute to elevated chloride absorption.²⁸

Although these results suggest a defect in THAL NaCl transport in the DS rat, others have suggested that increased sodium absorption by the collecting duct may contribute to the development of hypertension. Primary cell cultures of inner medullary collecting ducts isolated from DS rats absorbed more sodium than did cells isolated from DR rats.³⁴ However, we and others have found no difference in sodium absorption by cortical or inner medullary collecting ducts between DS and DR rats.²⁷

The reason for the different causes of salt-sensitive hypertension reported by various laboratories is unknown. They may be due to genetic isolation of different strains of DS animals, or there may be multiple causes with each one being necessary for the development of hypertension.

Although the Dahl rat has been used as the primary model of salt-sensitive hypertension, there are other intriguing models. One of the most interesting involves mice that express 1, 2, 3, or 4 copies of the gene encoding the A-type natriuretic peptide receptor (NPRA). The response of blood pressure to a high-salt diet in these mice correlates inversely with the number of NPRA genes. Interestingly, the animals with only 1 copy are hypertensive when on a normal-salt diet, and this is exacerbated when they are placed on a high-salt diet. In contrast, the animals with 4 copies of the gene actually show a decrease in blood pressure with a high-salt diet.³⁵ Although A-type natriuretic peptide normally inhibits both proximal tubule and collecting duct NaCl absorption,³⁶ little or nothing is known about the effects of manipulation of the NPRA gene on nephron transport.

DOCA-Salt Hypertension

The renal effects of this model are similar to hyperaldosteronism in humans, in which there is increased sodium absorption by the collecting duct with concomitant fluid retention and suppression of renin secretion. This model may also mimic relatively rare forms of hypertension such as those found in apparent mineralocorticoid excess, caused by a defect in 11 β -hydroxysteroid

dehydrogenase,³⁷ and glucocorticoid-remediable aldosteronism, caused by the presence of a chimeric protein containing the 5' region of 11 β -hydroxylase and the 3' region of aldosterone synthase.^{38,39} Thus, aldosterone synthesis is not regulated properly and plasma levels of aldosterone are elevated.

DOCA-salt hypertension is generated by excess administration of the synthetic mineralocorticoid DOCA, an aldosterone analog, and a high-salt diet, causing blood pressure to increase within 3 weeks. DOCA causes salt retention via stimulation of sodium reabsorption by the collecting duct system. In isolated perfused cortical collecting ducts, DOCA treatment causes a 30-fold increase in sodium absorption.⁴⁰ This can be explained by an increase in sodium channel activity because significant increases in luminal sodium conductance have been observed in adrenalectomized animals after DOCA treatment *in vivo*.⁴¹

In addition to their effects on luminal sodium channels, mineralocorticoids have also been shown to increase Na⁺,K⁺-ATPase activity in the collecting ducts.^{42,43} This is in part because of enhanced expression of the α - and γ -subunits of the Na⁺,K⁺-ATPase.⁴⁴ Enhanced Na⁺,K⁺-ATPase activity depends on luminal entry of sodium, because blockade of luminal sodium channels with amiloride prevents this effect.⁴¹ However, we do not know whether transcription or translation of Na⁺,K⁺-ATPase subunits is dependent on the initial increase in intracellular sodium.

In the inner medullary collecting duct, where peritubular osmolality is extremely high, DOCA treatment decreases sodium backflux from the interstitium to the lumen by decreasing paracellular permeability.⁴⁵ Therefore, the net effect of DOCA along the collecting duct is increased sodium reabsorption. DOCA increases not only net sodium reabsorption but also vasopressin-stimulated osmotic water permeability.⁴⁶ However, we do not presently know how DOCA increases water reabsorption.

Although the initial rise in blood pressure depends on sodium and fluid retention, several mechanisms have been implicated in the development and maintenance of hypertension in DOCA-salt-treated animals. These mechanisms include alterations in cerebral renin-angiotensin system, vasopressin activation, elevated sympathetic activity, and enhanced vascular reactivity. Plasma and tissue levels of vasoactive peptide hormones such as endothelin-1 (ET-1) are also increased in DOCA-NaCl-treated rats, contributing to the increased peripheral resistance. However, there is also upregulation of endothelin B receptors (ET_B) and endothelial NOS (eNOS) in the renal medulla, countering the effects of DOCA.^{47,48} The changes in urinary volume and sodium excretion caused by activation of ET_B receptors may be partly due to the effects of ET-1 on nephron transport.⁴⁷ We have shown that ET-1 can decrease proximal tubule fluid absorption, depending on its concentration,⁴⁹ and that ET-1 inhibits THAL NaCl absorption via ET_B receptors and release of NO.⁵⁰ Finally, ET-1 has been shown to inhibit vasopressin-stimulated osmotic water permeability in the cortical collecting duct.⁵¹ Therefore, it appears that ET-1 could attenuate hypertension in the DOCA-NaCl model by increasing sodium excretion.

In conclusion, these findings demonstrate the significance of different vasoactive compounds in regulating nephron transport and controlling blood pressure. However, important

questions regarding humoral control of nephron transport and its implication in hypertension are unanswered and intensive research in these areas is required.

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