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Pivotal Role of the Kidney in Hypertension

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Abstract

The kidneys play a pivotal role in causing some forms of hypertension and probably a permissive role in most, if not all, forms of hypertension. This concept of the critical role of the kidneys has been postulated for many years but has been solidified by the molecular unraveling of several monogenic forms of hypertension such as Liddle's syndrome, apparent mineralocorticoid excess and glucocorticoid-remedial aldosteronism. These and other hypertensive disorders cause sodium retention through excess Na reabsorption in the distal nephron. Some disorders of salt wasting and relative hypotension such as Bartter's syndrome, Gitelman's syndrome and pseudohypoaldosteronism also localize to Na transport abnormalities in the distal nephron. Hypertensive in the general population may also result from subtle abnormalities in sodium balance resulting from alterations in the distal nephron.

Key Indexing Terms

Liddle's syndrome; Gitelman's syndrome; Sodium; Genetics

Hypertension remains the most important modifiable risk factor for a variety of cardiovascular diseases including coronary heart disease, stroke, congestive heart failure, peripheral vascular disease and end-stage renal disease. In the United States, the prevalence of hypertension is very high and increases with age such that the prevalence exceeds 70% in both men and women aged 75 years or older. The level of awareness, treatment and consistency of blood pressure control are also known to be inadequate. Although we frequently think of hypertension as a public health problem in the developed countries, hypertension is clearly a huge and growing problem on a global basis.¹ The risk factors and causative mechanisms for hypertension include age, gender, body mass, diet, other environmental factors (such as stress) and probably many interacting genetic factors. Kidney disease is both a causative mechanism for hypertension and a result of uncontrolled hypertension. Here, the focus is on the pivotal role of the kidneys in causing hypertension; this is a complicated and far-reaching subject; so, the discussion will be selective with citation of only a few seminal studies.

The importance of the kidneys in causing hypertension has been known for decades, but Guyton² advanced the paradigm that the kidneys can not only cause certain forms of hypertension but also play an essential permissive role in almost all forms of hypertension. Guyton developed a complex and intricate computer model of the control mechanisms and feedback loops in blood pressure regulation, which helped to understand this role. The crux

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of the necessary permissive role of the kidney was the concept of the renal function curve and pressure natriuresis whereby the kidneys excrete more sodium as blood pressure becomes elevated. In this concept, renal function (at least the relationship between blood pressure and salt excretion) must be altered for elevated blood pressure to persist.

The kidneys regulate sodium balance by modulation of the rate of reabsorption of sodium filtered at the glomeruli. Approximately 24,000 mEq of sodium are filtered per day in a person with normal kidney function (normal glomerular filtration rate 120 mL/min $\times$ 1440 min/d $\times$ 140 mEq/L Na in plasma $\times$ 1L/1000 mL). All this filtered Na is reabsorbed except to excrete daily intake of Na; for a person in the usual steady-state balance on a 150-mEq Na diet, excretion would approximate 150 mEq. Approximately 60% of the sodium reabsorption occurs in the proximal tubule, another 30% in the thick ascending limb (TAL), 7% in the distal convoluted tubule (DCT) and the remaining 2% to 3% in the collecting duct leaving $\times$ 1% to be excreted. Despite the lower absolute Na reabsorption in the distal nephron (TAL, DCT and collecting duct), these nephron segments are where fine Na regulation occurs and, as will be discussed, where genetic mutations causing hypertension localize.

MONOGENIC FORMS OF HYPERTENSION

The critical role of the kidneys in hypertension has been solidified in more recent years by the molecular identification of monogenic forms of hypertension, all of which impinge on salt absorptive mechanisms in the kidney. Each of these disorders has also revealed aspects of normal physiology that were not readily apparent or completely accepted. Three monogenic hypertensive conditions illustrate these features, although other more complicated conditions could also be featured. First, Liddle's syndrome was described in the 1960s as an autosomal dominant form of hypertension associated with features suggestive of hyperaldosteronism (such as low potassium levels and in some cases metabolic alkalosis) but with low aldosterone levels.³ In the mid-1990s, Liddle's syndrome was discovered to be caused by various mutations in the C-terminal ends of beta and gamma subunits of the epithelial sodium channel, the transporter responsible for final regulation of sodium reabsorption in the distal nephron.^{4,5} The 3 homologous subunits of this channel had been cloned only shortly before this discovery. Subsequent elegant experiments demonstrated that these mutations in Liddle's syndrome were associated with binding regions (PY motifs) of molecules (Nedd4-2) involved in endocytosis of surface membrane channels⁶ (Figure 1). These mutations interfere with endocytosis resulting in active sodium channels remaining in the apical membrane causing persistent sodium retention even in the face of systemic signals and hormones, which would normally downregulate sodium reabsorption. These discoveries convincingly demonstrated that sodium retention in the distal nephron can cause hypertension. A significant body of work has subsequently been performed investigating the molecular details of the regulation of the epithelial sodium channel; the intense interest in this important biology results from this connection between sodium absorption and the resulting hypertension.

The second monogenic disorder illustrating the relationship between sodium absorption and hypertension is apparent mineralocorticoid excess. Apparent mineralocorticoid excess is an autosomal recessive disorder with low aldosterone but increased urine cortisol:cortisone metabolites. As background, a biological mystery arose when the mineralocorticoid receptor was found to be activated just as well by cortisol as by aldosterone, the physiologic mineralocorticoid agonist⁷: How could aldosterone regulate sodium absorption in the distal nephron when circulating cortisol levels were 1000 fold higher than aldosterone levels if they both activated the mineralocorticoid (or aldosterone) receptor? The syndrome of apparent mineralocorticoid excess explained this phenomenon when the genetic mutation

causing apparent mineralocorticoid excess was identified and explored. In mineralocorticoid responsive cells, such as the principal cells of the distal nephron, cortisol is prevented from activating the mineralocorticoid receptor by an enzyme that converts cortisol to cortisone (which does not activate the mineralocorticoid receptor nearly as well). This enzyme, 11 beta-hydroxysteroid dehydrogenase, is defective in patients with apparent mineralocorticoid excess, allowing cortisol to activate mineralocorticoid receptors without being metabolized^{8,9} (Figure 1). This enzyme is also inactivated by glycyrrhizic acid found in certain forms of licorice, accounting for occasional cases of hypertension caused by excess consumption of licorice products. Again this disorder illustrates that defects in the distal nephron can cause excess sodium retention accounting for hypertension, in this case by activation of the mineralocorticoid receptor, which could occur in other forms of hyperaldosteronism.

A monogenic hypertensive disorder is glucocorticoid-remedial aldosteronism. This disorder results from the crossover fusion of 2 homologous genes, aldosterone synthase and steroid 11 beta-hydroxylase, in the adrenal fasciculata.¹⁰ This fusion results in an abnormal gene product that is responsive to **adrenocorticotrophic hormone** (as cortisol production would usually be) but produces aldosterone and some other irregular steroid products. Suppressing **adrenocorticotrophic hormone** with dexamethasone decreases the abnormal aldosterone production, improving the blood pressure in patients with this unusual disorder. Even though this is not a renal disorder *per se*, the actions of aldosterone working in the distal nephron cause hypertension by sodium absorption. The 3 disorders discussed above focus attention on salt absorption in the distal nephron as a causative factor in hypertension. Other disorders such as activating mutations of the mineralocorticoid receptor or disorders of the with-no-lysine (K) kinases could be cited also to illustrate similar points.

SALT WASTING DISORDERS

Equally important in understanding the relationship between blood pressure and renal salt handling has been the molecular identification of genetic forms of salt wasting, which cause low blood pressure or a lower incidence of hypertension. Three conditions are notable: Bartter syndrome, Gitelman syndrome and pseudohypoaldosteronism. The latter condition results from an abnormal mineralocorticoid receptor but will not be further discussed here. Bartter and Gitelman syndromes were not clearly distinguished clinically until genetic characterization revealed them to be caused by distinct defects in 2 parts of the nephron, the TAL and the DCT, respectively. Bartter syndrome, classically resulting from a defect in the furosemide sensitive Na-K-2Cl cotransporter,¹¹ usually presents in neonates with hypokalemia, metabolic alkalosis and hypotension, which may be life threatening. The patients have all the characteristics of loop diuretic intake. Subsequent studies of patients with Bartter syndrome have demonstrated that this phenotype can result from defects in other transporters and associated proteins, which are physiologically coupled in the TAL: the renal outer medullary potassium channel in the apical membrane, the ClC-Kb chloride channel in the basolateral membrane and its associated protein barttin and the calcium sensing receptor on the basolateral membrane.¹² Again understanding these genetic defects has actually promoted the understanding of the physiologic coupling of transporters in this nephron segment.

Gitelman's syndrome presents with hypokalemia, variable metabolic alkalosis and low or normal blood pressure. These patients may present in adolescence or as adults with marked hypokalemia, although the extent of the hypokalemia is variable. This genetic abnormality results from a defect in the thiazide sensitive NaCl cotransporter in the DCT.¹³ Interestingly, defects in this gene are common, perhaps in as much as 1% of the population, and the patients with the clinical phenotype may frequently be compound heterozygotes.¹⁴ In other

words, affected individuals inherit 1 abnormal allele from their mother and a different abnormal allele of the same gene from their father. Although individuals with only 1 affected allele may be phenotypically normal, some of these individuals have been found to have increased sodium intake, perhaps representing an asymptomatic compensation to maintain salt homeostasis and normal blood pressure.

RELEVANCE OF GENETIC VARIATIONS TO GENERAL POPULATION

The possibility that relatively rare mutations in some of the genes discussed above could account for variations in blood pressure in the general population was recently examined. Lifton and coworkers, who have been the leader in identifying the monogenic hypertensive disorders above, examined the Framingham population for mutations in the Na-K-2Cl cotransporter, the NaCl cotransporter and renal outer medullary potassium channel. Carriers for mutations in these 3 genes had both systolic and diastolic blood pressures and the risk of hypertension substantially below that of the general population.¹⁵ This concept that rare but functionally significant mutations in a few genes could account for a significant amount of the variation in blood pressure in the population contrasts with the notion that common allele variations (perhaps with minor individual functional significance) account for blood pressure variation. Numerous studies have recently been completed or are in progress, which address the genetic causes of hypertension. Review of these is beyond the scope of this report, but the above concepts clearly link specific molecular entities and their genetic alterations with the physiology of sodium homeostasis and with clinical hypertension.

Do abnormalities in salt handling by the kidneys impact blood pressure in the general population? An interesting study in which we participated demonstrated that metabolic syndrome, which is well known to be associated with hypertension, is associated with salt sensitivity of blood pressure.¹⁶ In this study performed in China, approximately 1900 participants received 1 week of a low-sodium diet and 1 week of a high-sodium diet; blood pressure was carefully monitored and related to metabolic syndrome and its individual components. Those with the metabolic syndrome clearly had greater responses to variations in dietary sodium than did the individuals without metabolic syndrome. There was also a progressive increase in salt sensitivity with each additional metabolic syndrome component (abdominal obesity, elevated blood pressure, elevated triglyceride, low high-density lipoprotein and high glucose).¹⁶ This study, among others, illustrates the importance of salt sensitivity (and hence renal control of salt balance) in blood pressure regulation.

These selected examples demonstrate and reinforce the concept that Guyton proposed many years ago, the critical role of the kidneys and salt retention in generating and sustaining hypertension. This brief review has not touched on an additional critical concept that sodium retention likely causes additional secondary effects to maintain hypertension (through increased vascular resistance in part) independent of ongoing intravascular volume expansion. Also, hypertension likely does additional damage beyond just expanding intravascular volume. Nonetheless, the studies briefly discussed above and many others demonstrated that sodium retention by the kidneys is a major mechanism of hypertension.

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FIGURE 1.

Diagram illustrating defects in Liddle's syndrome and apparent mineralocorticoid excess. See text for details: (Adapted from Navar LG, Hamm LL. The kidney in blood pressure regulation. In: Schrier RW, editor. Atlas of diseases of the kidney. Philadelphia (PA): Current Medicine; 1999. p. 1.1–1.22).¹⁷