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Review Article

Sodium surfeit and potassium deficit: Keys to the pathogenesis of hypertension

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Abstract

The pathogenic role of Na^+ in primary hypertension is widely recognized but that of K^+ remains unappreciated. Yet, extensive evidence indicates that together, the body's dominant cations constitute the chief environmental factor in the pathogenesis of hypertension and its cardiovascular sequelae. In this Review, we provide a synthesis of the determinants of Na^+ retention and K^+ loss developing in the body as the Na^+-rich and K^+-poor modern diet interacts with kidneys intrinsically poised to conserve Na^+ and excrete K^+; and the molecular pathways utilized by these disturbances in the central nervous system and the periphery to increase sympathetic tone and vascular resistance, and establish hypertension. These fresh insights point to new directions for targeted pharmacotherapy of hypertension. The interdependency of Na^+ and K^+ in the pathogenesis of hypertension indicates that Na^+ restriction and increased K^+ intake are important strategies for the primary prevention and treatment of hypertension and its cardiovascular consequences. J Am Soc Hypertens 2014;8(3):203–213.

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Introduction

Contrary to isolated populations eating natural foods, contemporary societies are plagued by age-related increases in blood pressure and a lifetime risk of hypertension exceeding 90%. Such dramatic departure from normotension nowadays appears to arise largely from changes in environmental factors.[1]

Epidemiologic observations coupled with animal and human studies converge into the conclusion that K^+ deficiency augments the morbid impact of Na^+ excess on the pathogenesis of hypertension and associated cardiovascular complications.[2–5] Conversely, K^+ supplementation of animals or humans maintained on high Na^+ diets decreases blood pressure, and reduces cardiovascular and renal injury.[6–9] Indeed, in some studies, the vascular protection provided by K^+ was shown to be independent of its blood pressure-lowering effects.[10] Several years ago, we juxtaposed the evidence implicating Na^+ in the pathogenesis of hypertension with that for K^+.[1] On the strength of that analysis, we proposed that the chief environmental factor in the pathogenesis of primary hypertension and the associated cardiovascular disease is not an isolated surfeit of Na^+ or deficit of K^+ in the body, but the combination of the two derangements. The root cause is the interplay between the modern diet–rich in Na^+ and poor in K^+–and nonadapted kidneys that are intrinsically poised to conserve Na^+ and excrete K^+.

Since then, the proposal for a shared primacy of Na^+ and K^+ in the pathogenesis of primary hypertension and cardiovascular risk has been bolstered by novel insights on the manifold interactions of these electrolytes. Here we provide a synthesis of the determinants of Na^+ retention and K^+ loss prevailing in consumers of the modern diet, and the molecular pathways utilized by these disturbances in the central nervous system and the periphery to increase vascular resistance and establish hypertension.

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Na^+ Sensitivity and its Blockade by K^+

Linking Na^+ intake to hypertension conceptualized Na^+ sensitivity that refers to the blood pressure responsiveness to a short-term, sizable NaCl load or loss.[11–13] It is observed in approximately one-third of normotensives, serving as a harbinger of hypertension, and two-thirds of hypertensives. Sodium-sensitive individuals consuming a high-Na^+ diet appear to retain more Na^+ than Na^+-resistant subjects, indicating impaired renal Na^+ excretion. Declining glomerular filtration rate, aging, African descent, and obesity are associated with Na^+ sensitivity.

Dietary K^+ exerts a powerful, dose-dependent inhibitory effect on Na^+ sensitivity. Strikingly, an increase in dietary K^+ can even abolish Na^+ sensitivity in both normotensives and hypertensives.[1,14,15] Blockade of Na^+ sensitivity by K^+ reflects in part its natriuretic action. Sodium resistance in normotensives does not guarantee lasting normotension considering that over time, the vast majority of humans consuming a Na^+-rich and K^+-poor diet develop hypertension.

Linkage of the Modern Diet to Hypertension

Excess Na^+ and a K^+ deficit in the body have been detected in hypertensive animals and humans.[1,16–18] However, such reports have not been entirely consistent. Negative studies reflect several factors, including methodologic shortcomings, the altered distribution of Na^+ and K^+ among tissues (eg, increased Na^+ in vascular wall but reduced plasma Na^+ owing to plasma-volume contraction), and the relatively modest Na^+ gain and K^+ deficit in primary hypertension.

Despite the early presence of hypertension-promoting mechanisms, primary hypertension might not develop until late in life. Remarkably, this occurs even in monogenic defects in Na^+ excretion. Absent dietary adjustments, the delayed development of hypertension can reflect decline in renal function, diet and genome interactions (ie, epigenetic influences), and override of compensatory mechanisms with aging.[19]

The pressor effects of Na^+ excess depend on the associated counter anion, as only NaCl, the usual form consumed, causes hypertension. As indicated by insufficient weight gain, the Na^+ surplus must not obligate equivalent fluid retention. Retained Na^+ replaces, in part, intracellular K^+, which is then excreted as KCl in the urine. This Na^+-for-K^+ exchange is well documented in vascular smooth muscle (VSM) and skeletal muscle, most prominently in mineralocorticoid hypertension. Retained Na^+ is also stored extracellularly in skin, cartilage, and bone. Mobilization of Na^+ from extracellular stores can increase its level in body fluids and elicit a pressor response.[20] The linkage of the Na^+-rich and K^+-poor modern diet with the pathogenesis of hypertension is strongly supported by the blood pressure-lowering effects of diets with reverse cationic composition, that is, low in Na^+ and high in K^+.[21–24]

Na^+ Retention and K^+ Loss in Hypertension: Role of the Kidney

In primary hypertension, Na^+-retentive kidneys in concert with a Na^+-rich diet generate Na^+ excess. Concomitantly, ineffective K^+ conservation (renal and enteral) coupled with a K^+-poor diet engenders K^+ deficit. Stimulation of Na^+ transporters and the Na^+ pump (Na^+, K^+-ATPase) located at the luminal and basolateral membrane of the renal tubules, respectively, is key to these electrolyte deviations.[1]

Increased levels of sympathetic activity and angiotensin II as well as K^+ depletion stimulate Na^+ reabsorption in the proximal tubule and the thick ascending limb of Henle's loop by enhancing the activity of the luminal Na^+-H^+ exchanger.[1,25] The Na^+-Cl^- cotransporter in the distal tubule, the epithelial Na^+ channel (ENaC) in the collecting duct, and the ubiquitous Na^+ pump are stimulated by the aldosterone excess of primary hypertension causing Na^+ retention and K^+ loss.[26] Angiotensin II, independent of aldosterone, increases ENaC activity in the distal nephron. Experimental models of Na^+-sensitive hypertension exhibit enhanced expression of ENaC in the renal medulla.[1,27] The clinical effectiveness of thiazide diuretics in the management of hypertension attests to the pathogenic importance of Na^+ surfeit. Importantly, the resulting hypokalemia discounts the antihypertensive effect of thiazides.[28] Co-administration of K^+-sparing diuretics augments the antihypertensive effect of thiazide diuretics both by inhibiting ENaC activity and most likely, by maintaining a higher serum K^+ level.[29,30]

Mutations and polymorphisms in the α-adducin gene also stimulate the Na^+ pump. Contrary to their short-term actions, the long-term effects of K^+ depletion and increased levels of endogenous ouabain (EO) are to stimulate the activity and expression of the renal Na^+ pump, thereby promoting Na^+ retention.

The WNK (With No lysine Kinase) proteins participate in the molecular pathways that control sodium and potassium excretion, and therefore blood pressure.[31] Impaired release of corin, a serine protease produced by the cardiomyocyte that cleaves and activates atrial natriuretic peptide, causes Na^+ retention. Corin-deficient mice exhibit impaired natriuresis, hypertension, and cardiac hypertrophy.[32,33] Polymorphisms in the corin gene are associated with hypertension and heart failure in African Americans.

Genetic factors might account for approximately one-third of blood-pressure variability in the general population and involve a growing number of mutations and polymorphisms.[34] Variance in genes encoding proteins that alter renal Na^+ and K^+ transport, vascular-wall reactivity, sympathetic activity, and other processes, might predispose humans to hypertension or, alternatively, prevent or delay its development[35–41] (Table 1).