Salt-Sensitive Hypertension: New Players and Pathogenesis Revisited

Medical Grand Rounds
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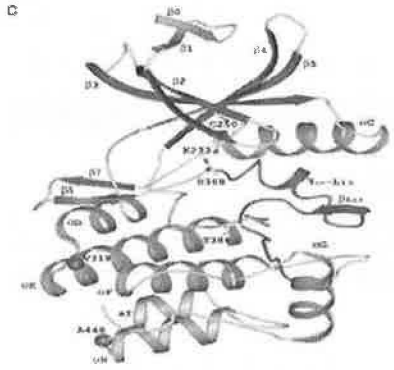
Ratio of Dietary Intake of Na and K

1:16

3:1



This is to acknowledge that Dr. Huang has not disclosed any financial interests or other relationships with commercial entities related directly or indirectly to this program. Dr. Huang will not discuss off-label use in this presentation.

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Research interests: genetic diseases of ion transport disorders, hypertension, WNK kinases in cardiovascular development, regulation of ion transport by anti-aging hormone Klotho.

Introduction

Hypertension is a major health problem in industrialized nations. The risk of cardiovascular, stroke, and renal disease is greatly increased in hypertensive individuals. Excessive salt intake exacerbates hypertension. The connection of salt intake and hypertension was first articulated by Ambard and Beaujard in a paper entitled "Causes de l'hypertension arterielle" (Ambard and Beaujard, 1904). Allen and colleagues in 1920's demonstrated the effectiveness of salt restriction in hypertension. In a paper by Allen, he said, "the morbidity and mortality from renal and vascular diseases would probably be reduced by a general abstinence from salt" (Allen, 1922). The definitive connection of salt intake to hypertension was established by Lewis Dahl and colleagues. In a series of careful metabolic studies published in JCI in 1950's (Dole et al., 1950; 1951; 1953), they clearly demonstrated the relationship between salt intake and hypertension, and thus the term "salt-sensitive hypertension". Figure 1 shows the correlation of average daily salt intake (measured by 24 hour urine excretion) with prevalence of hypertension in different geographic areas and among different races. Using inbreeding, Dahl and colleagues created the first genetically predisposed animal model for salt-sensitivity: Dahl salt-sensitive and salt-resistant rats (Dahl et al., 1962). Dahl and Heine (1975) further demonstrated that the genetic predisposition can be passed on by renal transplantation from susceptible to resistant animals.

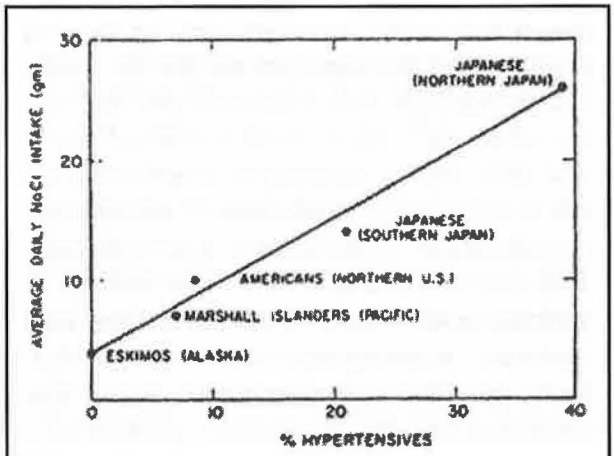


Figure 1

Pathogenesis of Salt-Sensitive Hypertension

Figure 2A shows the relationship of dietary sodium intake and blood pressure. While increased sodium intake causes elevated blood pressure in some individuals (salt-sensitive), it does not affect others (salt-resistant). Figure 2B shows the relationship of total body sodium and blood pressure. Interestingly, many

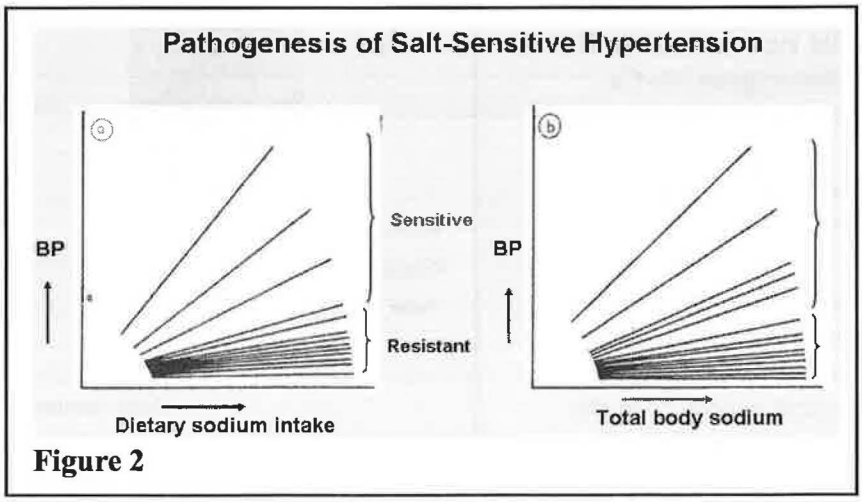


Figure 2

individuals with high total body sodium content are normotensive, indicating that other factor(s) besides sodium retention are also involved in the pathogenesis of salt-sensitive hypertension.

Edmondson et al (1975) reported that sodium content in peripheral blood cells are elevated in essential hypertensives. It was suggested that a similar excess of sodium in vascular smooth muscle cells causes vasoconstriction and hypertension (Blaustein, 1977). Others have found that endogenous ouabain-like compounds (cardiotonic substance, "CTS" in Figure 3) are present in human plasma (review by Hamlyn et al., 1996; Schoner, 2002). The level of these compound are elevated in hypertensives (Hamlyn et al., 1982; Manunta et al., 1999) or in individuals with high sodium intake (Hasegawa et al., 1987). It was believed that endogenous ouabain-like compounds inhibit the plasma membrane Na-K-ATPase to raise intracellular sodium (review by Hamlyn et al., 1996; Schoner, 2002) (Figure 3). Normally, Na-Ca exchangers use the Na^+ gradient (high extracellular vs low intracellular Na^+) to extrude intracellular Ca^{2+}. An increase in intracellular Na^+ would drive Na-Ca exchangers to operate in a reverse mode to bring in Ca^{2+} and cause an increase in intracellular Ca^{2+}. The increase in intracellular Ca^{2+} would cause smooth muscle cells to contract. This hypothesis is known as "cell-sodium (third factor) hypothesis". A strong support for this hypothesis was recently provided by Iwamoto et al (2004). They showed that infusion of a specific inhibitor of vascular Na-Ca exchangers lowers arterial blood pressure in salt-dependent hypertensive rat models, but not in other types of hypertensive or normotensive rats. In addition, salt loading increases blood pressure in wild type, but not in heterozygous Na-Ca exchanger-deficient mice.

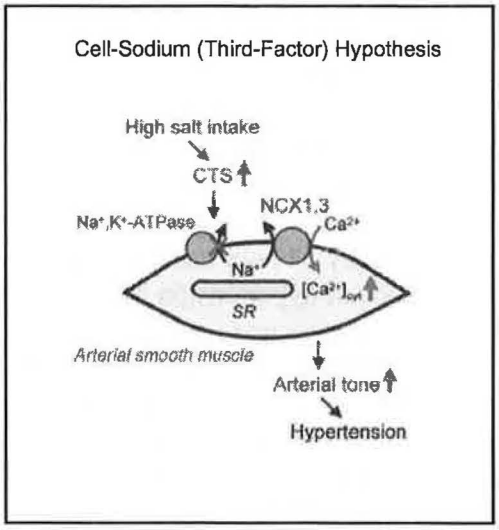


Figure 3

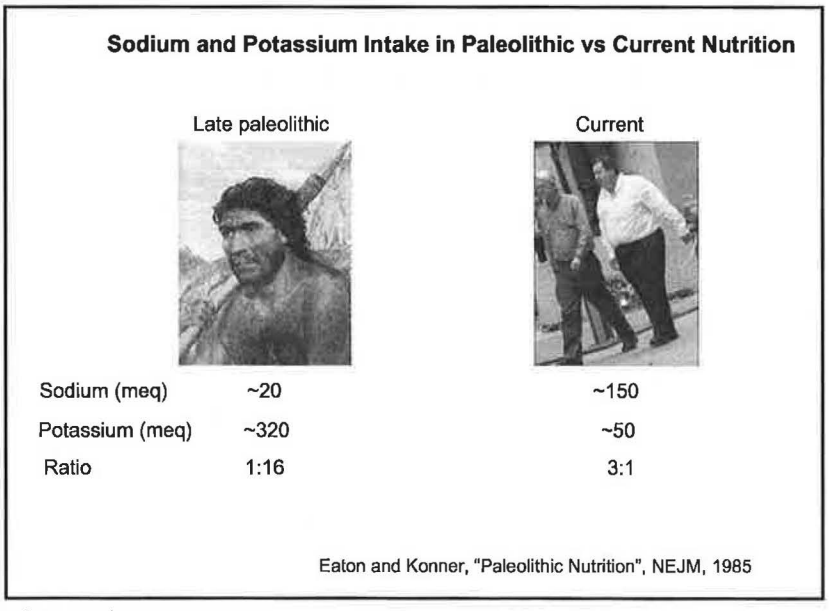


Figure 4

Role of Potassium in Hypertension

Another important factor in determining salt-sensitivity is dietary K^+ intake. Compared to our ancient ancestors in the paleolithic period, the

current North American diets contain ~7 times more sodium (Figure 4) (Eaton and Konner, 1985). Of the average daily sodium intake, only 10 % is naturally contained in food. Another 15% is added by consumers. The majority (~75 %) of the current dietary sodium intake is added by manufacturers. While Na^+ intake has increased (compared to our ancestors in the paleolithic period), K^+ intake has decreased. The decrease in K^+ intake is due to a decrease in consumption of fruits and vegetables. The ratio of dietary Na^+ to K^+ intake is ~1:16 for paleolithic humans and ~3:1 for current North Americans.
This represents a ~50-fold increase in the ratio of dietary intake of Na^+ vs K^+.

Relation of systolic BP with electrolytes

	Normal subjects	Hypertensive
Plasma Na	0.12	0.20
Exchangeable Na	0.04	0.44*
Total body Na		0.55*
Plasma K	0.17	-0.32*
Exchangeable K		-0.28*
Total body K		-0.28*
Plasma Na: K	-0.13	0.46*
Exchangeable Na: K		0.51*
Total body Na: K		0.60*

Correlation coefficients; * $p < 0.05$

Lever et al., Br Med J, 1981

Figure 5

Epidemiologic studies have established that K^+ intake is inversely related to the prevalence of hypertension independently of Na^+ intake (Langford, 1983). Figure 5 shows the relation of systolic blood pressure with electrolytes (adopted from Lever et al., 1981). Exchangeable Na^+ and K^+, plasma concentrations, and arterial blood pressure were measured in 91 patients with essential hypertension and 121 normal controls. The systolic BP (also diastolic BP, not shown) correlated positively with total body Na^+ and negatively with total body K^+ content. The correlation with total body Na^+ to K^+ ratio, however, was the best.

An international study of electrolyte excretion and blood pressure including 10,079 subjects from 52 centers of 32 countries ("Intersalt" study group, 1988) confirmed that "potassium excretion is negatively and independently correlated with blood pressure in individual subjects after adjustment for confounding variables". "The relation of urinary sodium to potassium ratio to blood pressure in individual subjects followed a pattern similar to that for sodium but more strongly and consistently". In support of the importance of K^+ in lowering blood pressure, Kaplan et al (1985) showed that potassium supplementation (KCl, 60 meq) decreases blood pressure in hypertensive patients with diuretic-induced hypokalemia.

It is known that blacks have high prevalence of hypertension and (compared to that in whites) hypertension in blacks is more "salt-sensitive". Morris et al (1998) studied the effects of dietary K^+ intake on salt-sensitivity in 24 normotensive blacks and 14 whites. They found that at 30 meq daily K^+ intake, 79 % of blacks and 36 % whites are salt-sensitive (BP increased by > 3 mm Hg on 250 meq NaCl loading for 1 week) (Figure 6). Increasing dietary K^+ intake to 70 meq

attenuated salt-sensitivity in both blacks and whites and to 120 meq abolished it. They concluded that the heightened salt-sensitivity in blacks is due to their relatively lower dietary potassium intake.

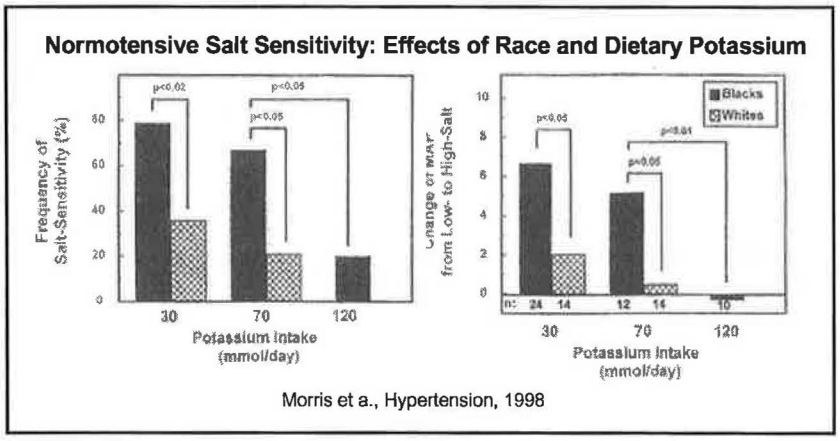


Figure 6

Krishna et al (1991) studied the effects of low dietary intake on blood pressure and urinary Na^+ excretion. Figure 7 shows blood pressure in 11 hypertensive subjects ingesting either 96 mM or 16 mM of KCl daily for 10 days. Figure 8 shows daily urinary K^+ and Na^+ excretion in these subjects. The elevation of blood pressure by low K^+ intake can be prevented by decreasing daily Na^+ intake from 90 mM to 10 mM. Thus, low dietary K^+ intake elevates blood pressure by increasing renal Na^+ reabsorption.

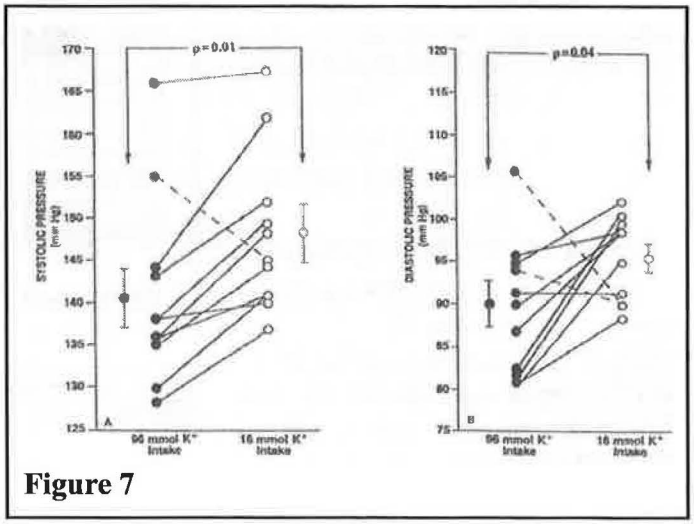


Figure 7

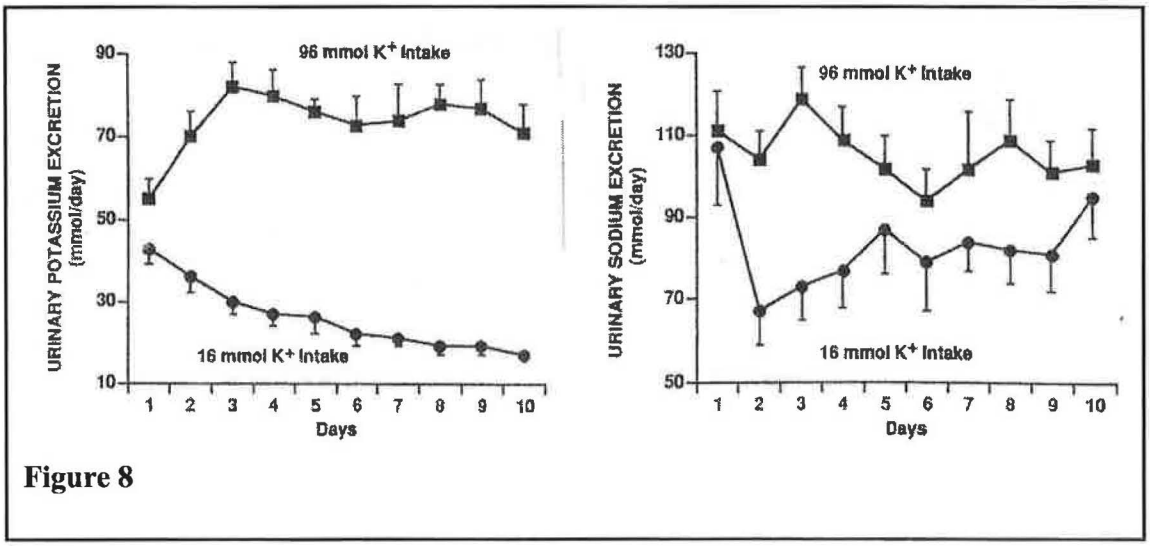


Figure 8

In another paper, Krishna et al (1989) conducted a randomized crossover study to examine the effects of 90 mM vs 10 mM daily K^+ intake on 10 healthy normotensive subjects . They showed that daily K^+ intake at 10 mM for 10 days increased mean arterial blood pressure by ~5 mm Hg. Daily K^+ intake at 90 mM did not alter mean arterial blood pressure. Along with the increase in blood pressure on low K^+ intake, both urinary Na^+ excretion and plasma aldosterone decreased significantly. Low K^+ intake, however, did not affect glomerular filtration rate and renal plasma flow measured by inulin and hippurate clearance, respectively.

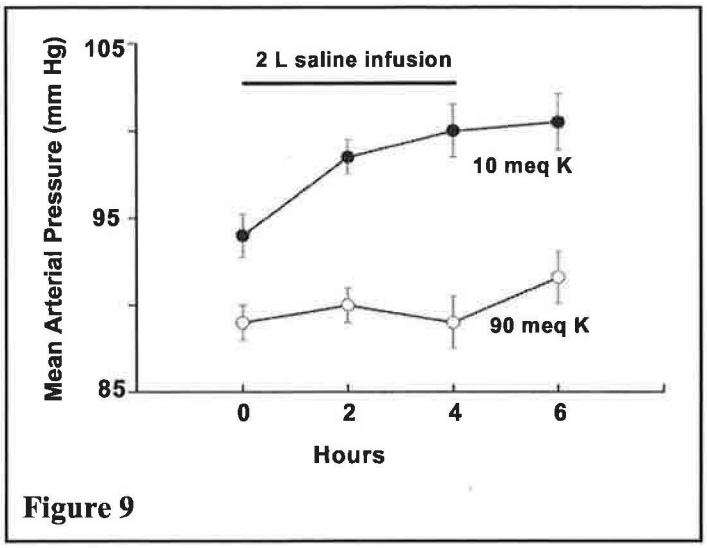


Figure 9

Nor did it affect circulating levels of vasopressin, catecholamines, atrial natriuretic peptide. Krishna et al further examined the response of these subjects to acute saline infusion. Figure 9 shows that baseline mean arterial blood pressure for subjects on 10 mM K^+ intake was higher than that for subjects on 90 mM K^+. In response to 2 liters of saline infusion, mean arterial blood pressure rose in subjects on low K^+ intake but not in those on normal K^+ intake. These results indicate that, in addition to Na^+ retention, low K^+ intake increases cardiovascular contractility (i.e., increases peripheral vascular resistance, increases cardiac output, and/or decreases venous capacitance).

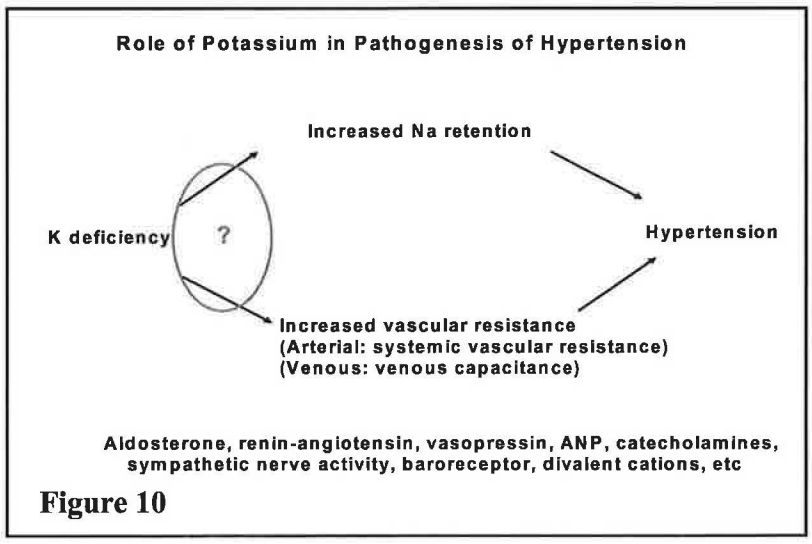


Figure 10

Overall, the relationship between K^+ deficiency and elevated blood pressure is quite clear. K^+-deficiency increases blood pressure by increasing renal Na^+ reabsorption as well as cardiovascular contractility (Figure 10). The mechanism by which K^+-deficiency increases renal Na^+ reabsorption and cardiovascular contractility remains elusive. Recent evidence suggests that WNK1 kinase may be the missing link between K^+-deficiency and increased renal Na^+ reabsorption and cardiovascular contractility.

WNK Kinases and Pseudohypoaldosteronism

WNK (with no lysine [K]) kinases are a new family of large serine-threonine protein kinases conserved in multicellular organisms with an atypical placement of the catalytic lysine (Figure 11) (Xu et al., 2000). There are four mammalian WNK family members (Verissimo et al., 2001). WNK1, the first member identified, is over 2100 amino acids long. It contains a ~270 amino acid kinase domain located near the amino terminus (e.g., amino acids 218-491 of rat WNK1). WNK2, 3, and 4 are products of different genes and range from 1200 to 1600 amino acids in length (Xu et al., 2000; Verissimo et al., 2001). WNK4 is widely expressed in epithelial tissues. WNK1 is ubiquitous. An alternatively spliced WNK1 isoform is specifically expressed in kidney, thus kidney specific (KS)-WNK1 (O'Reilly et al., 2003; Delaloy et al., 2003). The ubiquitous WNK1 is also known as long WNK1 (L-WNK1). KS-WNK1 is an antagonist of L-WNK1 (Subramanya et al., 2006; Lazrak et al., 2006).

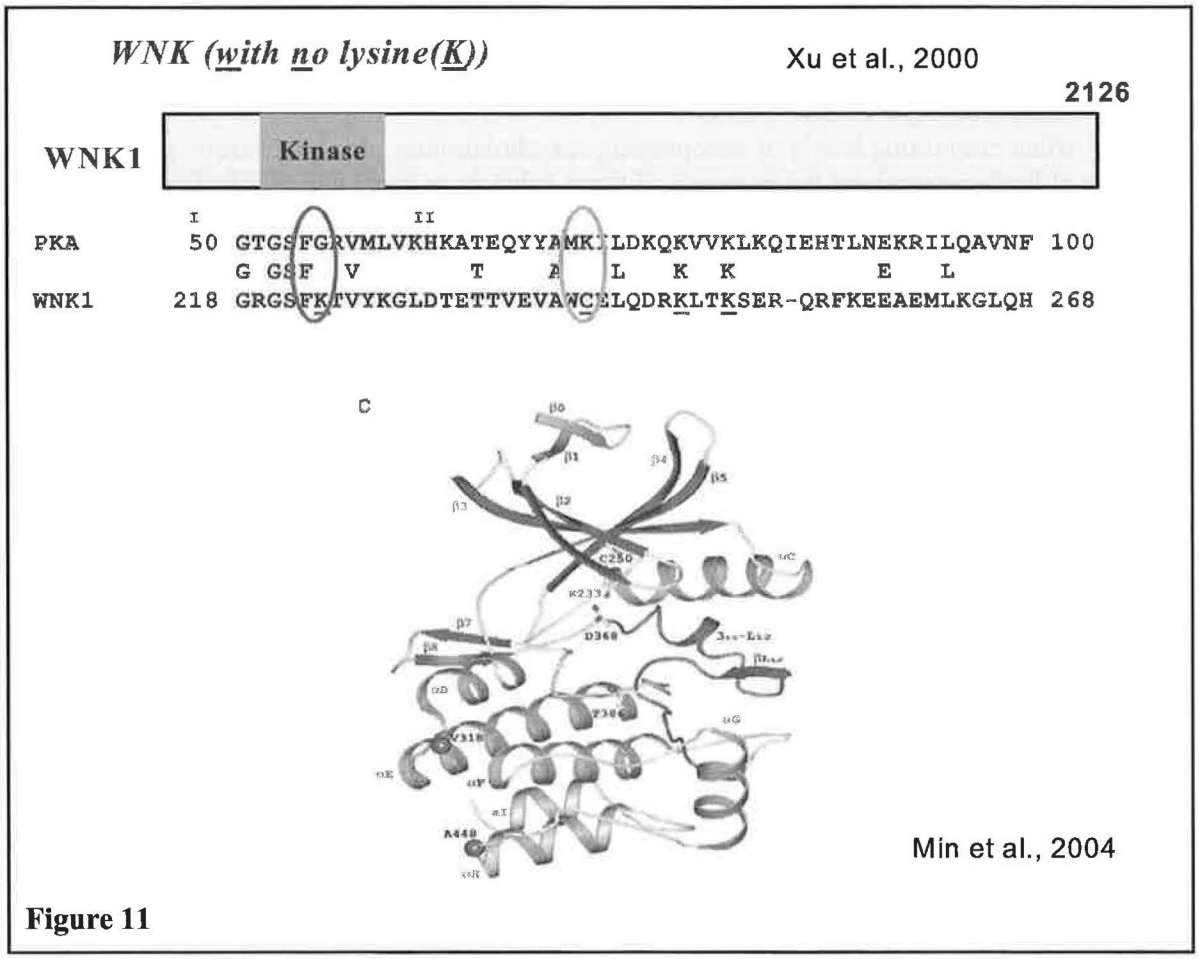


Figure 11

Pseudohypoaldosteronism type II (PHA II) is an autosomal-dominant disease characterized by hypertension, hyperkalemia, hyperchloremic metabolic acidosis, and normal glomerular filtration rate (Gordon, 1986). PHA II is also know as Gordon's syndrome. Prior to Gordon's description in 1970, several papers had reported isolated cases of the disease (Paver and Pauline, 1964; Stokes et al., 1968; Arnold and Healy, 1969). In a seminal paper published in 1981, Schambelan et al investigated the pathogenesis of Gordon's syndrome studying a 23 year-old male with hyperkalemia and hypertension (Schambelan et al, 1981). They found that renal clearance of K^+ in the patient was low despite a normal NaCl intake. Renal K^+ clearance remained low during intravenous infusion of NaCl and with superimposed chronic mineralocorticoid administration. Plasma renin activity was suppressed. Plasma and 24 urine aldosterone were elevated. Hypertension and hyperkalemia were ameliorated by 50 mg HCTZ per day alone. Because of hyperkalemia despite high level of aldosterone, Schambelan and coworkers proposed that the disease be named pseudohypoaldosteronism type II.

The nomenclature of PHA II deserves clarification. In the renal distal tubule, aldosterone binds to the mineralocorticoid receptor and stimulates sodium reabsorption through the epithelial Na^+ channel ENaC . Na^+ reabsorption in the distal tubule establishes the electrical driving force for potassium secretion. Aldosterone also stimulates sodium absorption and potassium excretion in extra-renal tissues such as colon. Thus, the increased action of aldosterone will lead to sodium retention and potassium wasting, and vice versa.

Pseudohypoaldosteronism describes conditions of apparent hypoaldosteronism despite normal to high circulating levels of aldosterone. There are two separate clinical syndromes of PHA. Type 1 PHA (PHA I) reflects the apparent lack of aldosterone effect on sodium reabsorption and potassium secretion, and thus features hypotension and hyperkalemia (Lifton et al., 2001). There are autosomal dominant and autosomal recessive forms of the disease caused by mutations of the mineralocorticoid receptor and ENaC, respectively (Lifton et al., 2001). Gordon's syndrome is a second type of PHA based on the clinical finding of hyperkalemia as the phenotype of apparent hypoaldosteronism. However, unlike PHA I, patients with Gordon's syndrome have hypertension. Some investigators prefer the name "Familial Hyperkalemic Hypertension" for Gordon's syndrome to distinguish its hypertensive phenotype from the hypotensive phenotype in PHA I.

Recently, Wilson et al reported that mutations of *WNK1* and *WNK4* cause PHAII (Wilson et al., 2001). Mutations in the *WNK1* gene are large deletions of the first intron leading to increased expression. Mutations in the *WNK4* gene are missense mutations in the coding sequence outside the protein kinase domain.

Identification of WNK1 and WNK4 gene mutations as causes of PHA II has accelerated recent studies examining the pathogenesis of PHA II. Figure 12 and 13 show pathogenesis of hypertension and hyperkalemia caused by mutations of WNK4 and WNK1, respectively.

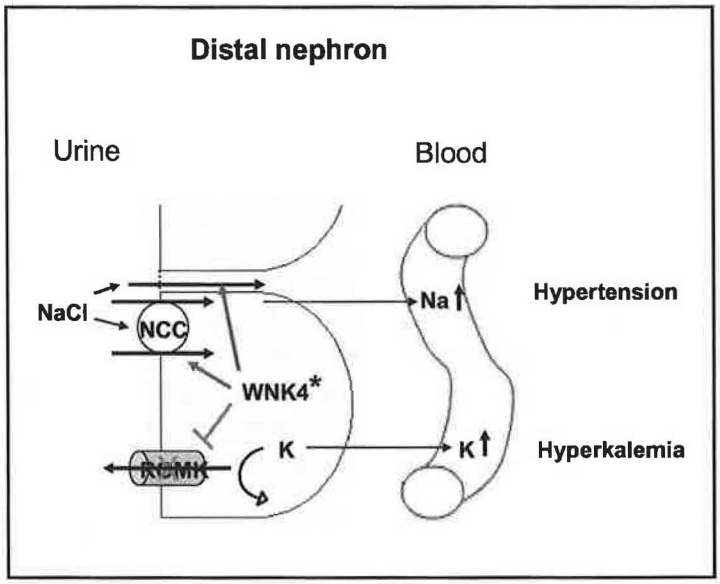


Figure 12

Mutations of WNK4 increase Na^+ reabsorption via the thiazide-sensitive Na-Cl co-transporter (NCC) and paracellular pathways (Figure 12) (Yang et al., 2003; Wilson et al., 2003; Yamauchi et al., 2004). Mutations of WNK4 cause hyperkalemia by inhibiting K^+ secretion through the K^+ channel ROMK in the distal nephron (Kahle et al., 2004).

Normally, L-WNK1 activates the epithelial Na channel ENaC and inhibits ROMK (Figure 13). KS-WNK1 is an antagonist of L-WNK1 with respects to its effects on ROMK and ENaC. Mutations of WNK1 gene in PHA II are deletions of the first intron leading to increased expression of L-WNK1. Thus, patients with PHA II have increased ratio of L-WNK1/KS-WNK1, which leads to increased Na^+ reabsorption and inhibition of K^+ secretion in the distal nephron (Xu et al., 2005; Lazrak et al., 2006).

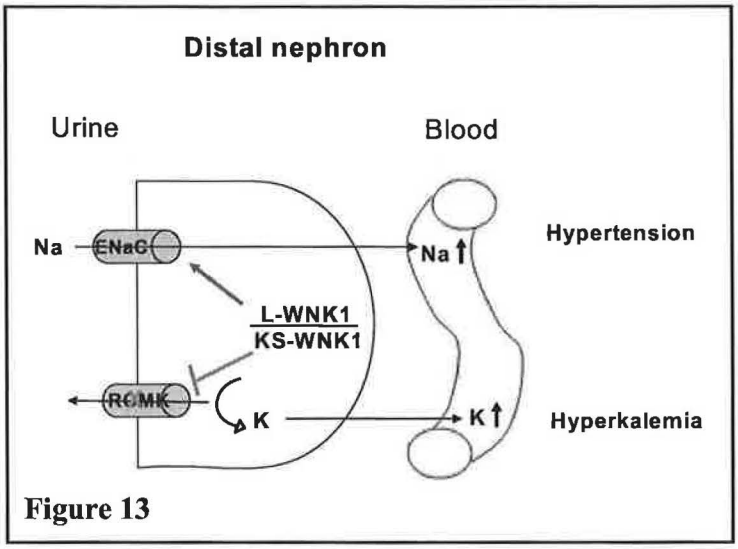


Figure 13

Aldosterone increases Na^+ reabsorption through ENaC, which increases lumen-negative transepithelial potential difference (PD) to stimulate K^+ secretion through ROMK. If this were the only mechanism for regulation of Na^+ and K^+ transport in the distal nephron, one would see that increased Na^+ reabsorption would be always coupled to increased K^+ secretion. However, we know that majority of salt-sensitive hypertension does not have primary hypokalemia. Also, as discussed above, potassium supplementation abolishes the salt-sensitive hypertension. How do we explain for this relationship between Na^+ and K^+ homeostasis? We found that WNK1

plays a key role .

As shown in Figure 14, urinary K^+ excretion decreases during K^+ deficiency to maintain K^+ homeostasis. We found that this occurs with increased and decreased expression of L-WNK1 and KS-WNK1, respectively (Lazrak et al., 2006). The increased L-WNK1/KS-WNK1 ratio results in decreased K^+ secretion through ROMK, but at the expense of increased Na^+ retention and hypertension.

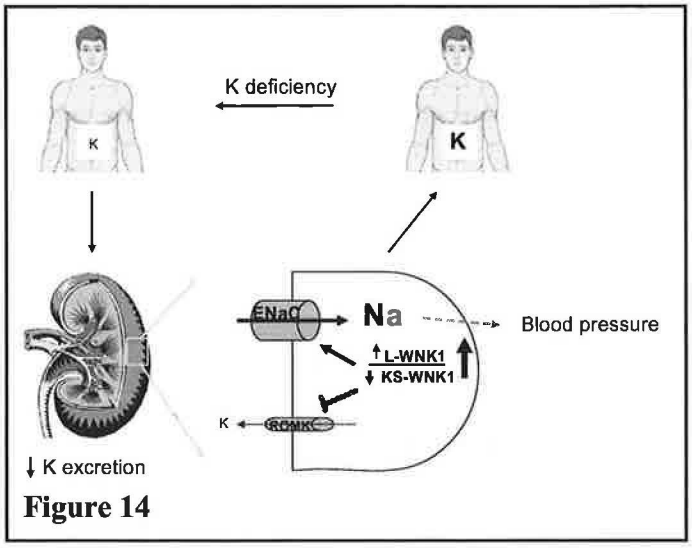


Figure 14

WNK1 is ubiquitous. The increase in L-WNK1 expression in K^+ deficiency is not limited to the kidney. Our results showed that K^+ deficiency increases L-WNK1 expression in leukocytes and in blood vessels. WNK1 activates the Na-K-2Cl cotransporter, NKCC1 (Anselmo et al., 2006). The activity of NKCC1 is important for vascular tone (Figure 15). Knockout of NKCC1 in mice causes hypotension and decrease in vascular smooth muscle tone (Meyer et al., 2002). Thus, WNK1 activates NKCC1 to increase vascular smooth muscle tone. In addition, mice with homozygous WNK1 knockout die *in utero* before embryonic day 13 (Zambrowicz et al., 2003), suggesting that WNK1 is crucial for cardiovascular development. Thus, the increased L-WNK1 expression in K^+ deficiency may have chronic as well as acute effects on cardiovascular system.

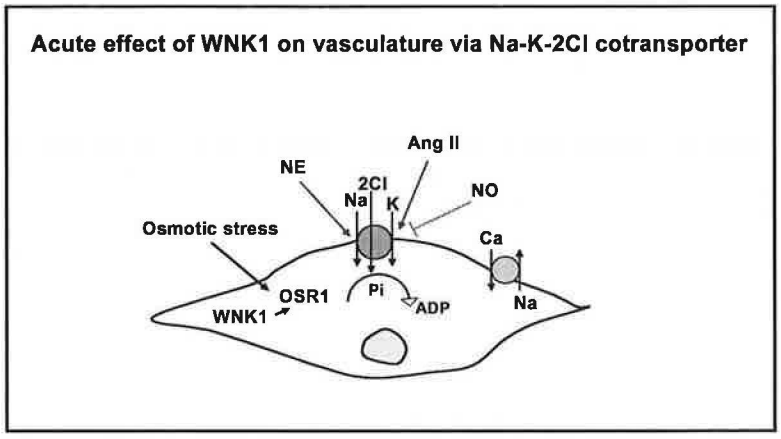


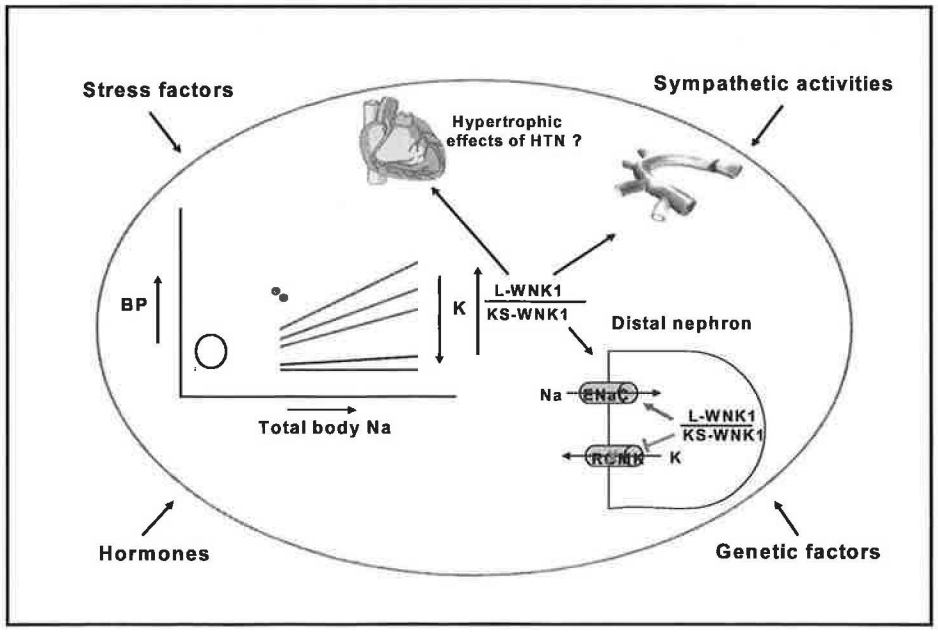
Figure 15

Summary

Hypertension is a recent health problem in the human history. The increase in prevalence of hypertension in the past 50 years coincides with the increase in salt (sodium) intake. Sodium is the major determinant of extracellular volume. However, the sensitivity of developing hypertension in response to increased salt intake varies for each individual. This variability in the

salt-sensitivity resides in differences of the ability of kidney to excrete sodium and/or the ability of cardiovascular system to accommodate volume expansion. Along with the increase in sodium intake in the past half-century, potassium intake has markedly decreased. The decrease in potassium intake is strongly correlated with the increase in the prevalence of hypertension. Potassium supplement abolishes salt loading-induced increase in BP. Recent evidence suggests that the ratio of long vs kidney-specific WNK1 kinase may be a key player in mediating the effect of increased potassium intake on lowering BP. K^+ deficiency leads to an increase in L-WNK1/KS-WNK1 ratio, causing renal Na^+ retention. Conversely, K^+ supplementation suppresses L-WNK1/KS-WNK1 ratio, resulting in Na^+ excretion. The decrease in L-WNK1 in blood vessels and heart causes vasodilation and decrease in cardiac contractility, respectively. Over time, the effects of L-WNK1 on heart and blood vessels may lead to hypertrophy and vasculopathy, further increasing blood pressure and its consequences.

Essential hypertension developed in low salt intake (~50 meq) is considered non-salt dependent. Yet, many non-salt dependent hypertensive individuals respond to diuretic treatments. The physiological requirement for sodium in humans is ~10 meq. Thus, all hypertension, except secondary forms, may be considered salt-sensitive. The fact that potassium supplement decreases BP in all comers of essential hypertensive subjects, salt-sensitive or not, supports the idea of a common pathogenesis for salt-sensitive and "non-salt sensitive" hypertension. The increased ratio of L-WNK1 to KS-WNK1 in kidney and cardiovascular system from our sodium-excess potassium-deficient diet is central to the pathogenesis of all essential hypertension. If so, one would predict that all essential hypertension could be reversed by a low Na^+, high K^+ diet if given at the early stage before any renal and cardiovascular pathology occurs. Many other factors also affect the response of the kidney and cardiovascular system to Na^+ and K^+, and thus important in the development and progression of hypertension.



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