REVIEW ARTICLE

MECHANISMS OF DISEASE

Sodium and Potassium in the Pathogenesis of Hypertension

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HYPERTENSION AFFECTS APPROXIMATELY 25% OF THE ADULT POPULATION worldwide, and its prevalence is predicted to increase by 60% by 2025, when a total of 1.56 billion people may be affected.[1] It is the major risk factor for cardiovascular disease and is responsible for most deaths worldwide.[2] Primary hypertension, also known as essential or idiopathic hypertension, accounts for as many as 95% of all cases of hypertension.[3]

Primary hypertension results from the interplay of internal derangements (primarily in the kidney) and the external environment. Sodium, the main extracellular cation, has long been considered the pivotal environmental factor in the disorder. Numerous studies show an adverse effect of a surfeit of sodium on arterial pressure.[4-7] By contrast, potassium, the main intracellular cation, has usually been viewed as a minor factor in the pathogenesis of hypertension. However, abundant evidence indicates that a potassium deficit has a critical role in hypertension and its cardiovascular sequelae.[8-10] In this review, we examine how the interdependency of sodium and potassium influences blood pressure. Recent evidence as well as classic studies point to the interaction of sodium and potassium, as compared with an isolated surfeit of sodium or deficit of potassium, as the dominant environmental factor in the pathogenesis of primary hypertension and its associated cardiovascular risk. Our review concludes with recent recommendations from the Institute of Medicine concerning the dietary intake of sodium and potassium.

DIETARY SODIUM AND HYPERTENSION

Primary hypertension and age-related increases in blood pressure are virtually absent in populations in which individual consumption of sodium chloride is less than 50 mmol per day; these conditions are observed mainly in populations in which people consume more than 100 mmol of sodium chloride per day.[3] The International Study of Salt and Blood Pressure (INTERSALT), which included 10,079 subjects from 32 countries, showed a median urinary sodium excretion value of 170 mmol per day (approximately 9.9 g of sodium chloride per day).[11] Although individual sodium intake in most populations throughout the world exceeds 100 mmol per day, most people remain normotensive. It appears, then, that sodium intake that exceeds 50 to 100 mmol per day is necessary but not sufficient for the development of primary hypertension.

In an analysis across populations, the INTERSALT researchers estimated an increase in blood pressure with age over a 30-year period (e.g., from 25 to 55 years of age); mean systolic blood pressure was 5 mm Hg higher and diastolic blood pressure was 3 mm Hg higher when sodium intake was increased by 50 mmol per day. In an analysis within single populations, a positive correlation between sodium intake and blood pressure was also detected after adjustment for a number of potentially confounding variables.[11]

Humans share 98.4% genetic identity with chimpanzees, and a landmark interventional study in chimpanzees showed that adding up to 15 g of sodium chloride to the diet per day increased systolic blood pressure by 33 mm Hg and diastolic blood pressure by 10 mm Hg; the increases were reversed after withdrawal of the sodium chloride supplement.[12] In the Dietary Approaches to Stop Hypertension (DASH) sodium study, a reduction in sodium intake caused stepwise decreases in blood pressure. Levels of sodium intake studied in random order were approximately 150 mmol per day, 100 mmol per day, and 50 mmol per day.[13] A meta-analysis of randomized controlled trials lasting at least 4 weeks concluded that reducing sodium intake by 50 mmol per day decreases systolic blood pressure by an average of 4.0 mm Hg and diastolic blood pressure by an average of 2.5 mm Hg in hypertensive subjects and decreases systolic blood pressure by an average of 2.0 mm Hg and diastolic blood pressure by an average of 1.0 mm Hg in normotensive subjects.[14]

POTASSIUM CONTENT OF SODIUM-RICH DIETS

As compared with diets based on natural foods, diets based on processed foods are high in sodium and low in potassium.[3,10] For example, two slices of ham (57 g) contain 32.0 mmol of sodium and 4.0 mmol of potassium, and a cup of canned chicken noodle soup contains 48.0 mmol of sodium and 1.4 mmol of potassium. Conversely, diets containing abundant fruits and vegetables are sodium-poor and potassium-rich.[3,10] For example, an orange (131 g) contains no sodium and 6.0 mmol of potassium, and a cup of boiled peas contains 0.3 mmol of sodium and 9.8 mmol of potassium. Isolated populations that eat natural foods have an individual potassium intake that exceeds 150 mmol per day and a sodium intake of only 20 to 40 mmol per day (the ratio of dietary potassium to sodium is >3 and usually closer to 10).[6,8,10] By contrast, people in industrialized nations eat many processed foods and thereby ingest 30 to 70 mmol of potassium per day and as much as 100 to 400 mmol of sodium per day (the usual dietary potassium:sodium ratio is <0.4).[3,10]

Hypertension affects less than 1% of people in isolated societies but approximately one third of adults in industrialized countries.[3,10] Differences in the prevalence of hypertension among these populations have usually been attributed to differences in the amounts of dietary sodium consumed, but they could also reflect differences in potassium intake. The movement of isolated populations into more urban areas is consistently associated with age-related increases in blood pressure and a rise in the prevalence of hypertension as the dietary potassium:sodium ratio decreases in the new location.[15,16]

VASCULAR EFFECTS OF POTASSIUM DEPLETION

Early reports of the vasodilatory or blood-pressure–lowering properties of both potassium depletion and potassium supplementation[17,18] delayed recognition of the effects of potassium depletion that are toxic to the blood vessels. These studies of the effects of a low intake of potassium on blood pressure, performed mostly in young rats, also involved a low intake of sodium and chloride. Potassium restriction causes a deficit in cellular potassium that triggers cells to gain sodium in order to maintain their tonicity and volume.[19] The deficits of potassium, sodium, and chloride in the body imposed by those early studies contracted both the intracellular and extracellular compartments, thereby engendering a decrease in blood pressure.[18,20] Subsequent studies in rats showed that the pressor effect of potassium depletion requires abundant consumption of sodium chloride (e.g., 4.5 g of sodium chloride per 100.0 g of dietary intake).[21]

Population studies have shown an inverse relation of potassium intake to blood pressure, the prevalence of hypertension, or the risk of stroke.[8,22-25] After adjusting for potentially confounding variables, the INTERSALT researchers estimated that a decrease in potassium excretion by 50 mmol per day was associated with an increase in systolic pressure of 3.4 mm Hg and an increase in diastolic pressure of 1.9 mm Hg. The urinary potassium:sodium ratio in the INTERSALT study had a significant, inverse relation with blood pressure. This ratio bore a stronger statistical relationship to blood pressure than did either sodium or potassium excretion alone.[11] As compared with whites, blacks have a higher prevalence of hypertension and lower potassium intake; sodium intake among whites and blacks is similar.[10,23] For example, in the Evans County

Study, 23% of whites and 38% of blacks had a diastolic pressure of 90 mm Hg or higher. The 24-hour urinary potassium excretion averaged 40 mmol per day for whites and 24 mmol per day for blacks.[26]

In clinical studies, a diet low in potassium (10 to 16 mmol per day) coupled with the participants' usual sodium intake (120 to 200 mmol per day) caused sodium retention and an elevation of blood pressure; on average, systolic pressure increased by 6 mm Hg and diastolic pressure by 4 mm Hg in normotensive subjects, and systolic pressure increased by 7 mm Hg and diastolic pressure by 6 mm Hg in hypertensive subjects.[24,25]

CARDIOVASCULAR EFFECTS OF POTASSIUM SUPPLEMENTATION

Studies have shown that increasing the potassium intake of hypertensive rats that were fed high-sodium diets lowered blood pressure, reduced the incidence of stroke and stroke-related death, and prevented cardiac hypertrophy, mesenteric vascular damage, and renal injury.[27,28] In one of the studies, these benefits were independent of the blood pressure–lowering effect of the diet.[27]

Kempner's rice–fruit diet, which was introduced in the 1940s, was rich in potassium and extremely low in sodium. This diet was widely used in treating hypertension and congestive heart failure.[29] Subsequently, many studies examined the effect of potassium on blood pressure and most of them identified a salutary effect.[8,30] A meta-analysis of 33 randomized trials that evaluated the effects of an increased potassium intake on blood pressure concluded that potassium supplementation (≥60 mmol per day in all but 2 trials) lowered systolic pressure by an average of 4.4 mm Hg and diastolic pressure by an average of 2.5 mm Hg in hypertensive subjects and lowered systolic pressure by an average of 1.8 mm Hg and diastolic pressure by an average of 1.0 mm Hg in normotensive subjects.[31] This effect was independent of a baseline potassium deficiency, and it was greater at higher levels of sodium excretion (≥160 mmol per day) and in trials in which at least 80% of the subjects were black.

Potassium supplementation can reduce the need for antihypertensive medication. One study showed that with an increased dietary potassium intake in hypertensive subjects, 81% of the subjects needed less than half of the baseline medication and 38% required no antihypertensive medication for blood-pressure control, as compared with 29% and 9%, respectively, in the control group at 1 year of follow-up.[32]

In the DASH trial, a diet rich in fruits and vegetables, as compared with the typical American diet, reduced systolic pressure in the 133 hypertensive subjects by 7.2 mm Hg and diastolic pressure by 2.8 mm Hg, at a constant level of sodium intake.[33] The potassium content of the diet of fruits and vegetables was more than twice as high as that of the typical American diet; therefore, its higher potassium:sodium ratio probably accounted for most of the observed reduction in blood pressure.

Sodium sensitivity, defined as an increase in blood pressure in response to a higher sodium chloride intake than that in the baseline diet, occurs in many normotensive and hypertensive subjects[34]; in normotensive subjects, sodium sensitivity appears to be a precursor of hypertension. Dietary potassium has been shown to exert a powerful, dose-dependent inhibitory effect on sodium sensitivity. With a diet that was low in potassium (30 mmol per day), 79% of normotensive blacks and 36% of normotensive whites had sodium sensitivity. Supplementation with 90 mmol of potassium bicarbonate per day resulted in sodium sensitivity in only 20% of blacks; this proportion matched that of whites when they received supplementation with only 40 mmol of potassium bicarbonate per day. An increase in dietary potassium can even abolish sodium sensitivity in both normotensive and hypertensive subjects.[10,34]

LACK OF ADAPTATION OF THE KIDNEYS TO THE MODERN DIET

Human kidneys are poised to conserve sodium and excrete potassium. Prehistoric humans, who consumed a sodium-poor and potassium-rich diet, were well served by this mechanism.[5] With such a diet, sodium excretion is negligible and potassium excretion is high, matching potassium intake. The kidneys account for 90% or more of potassium loss, with the remainder exiting through the fecal route. This mechanism, however, is unfit for the sodium-rich and potassium-poor modern diet. The end result of the failure of the kidneys to adapt to this diet is an excess of sodium and a deficit of potassium in hypertensive patients (Fig. 1).

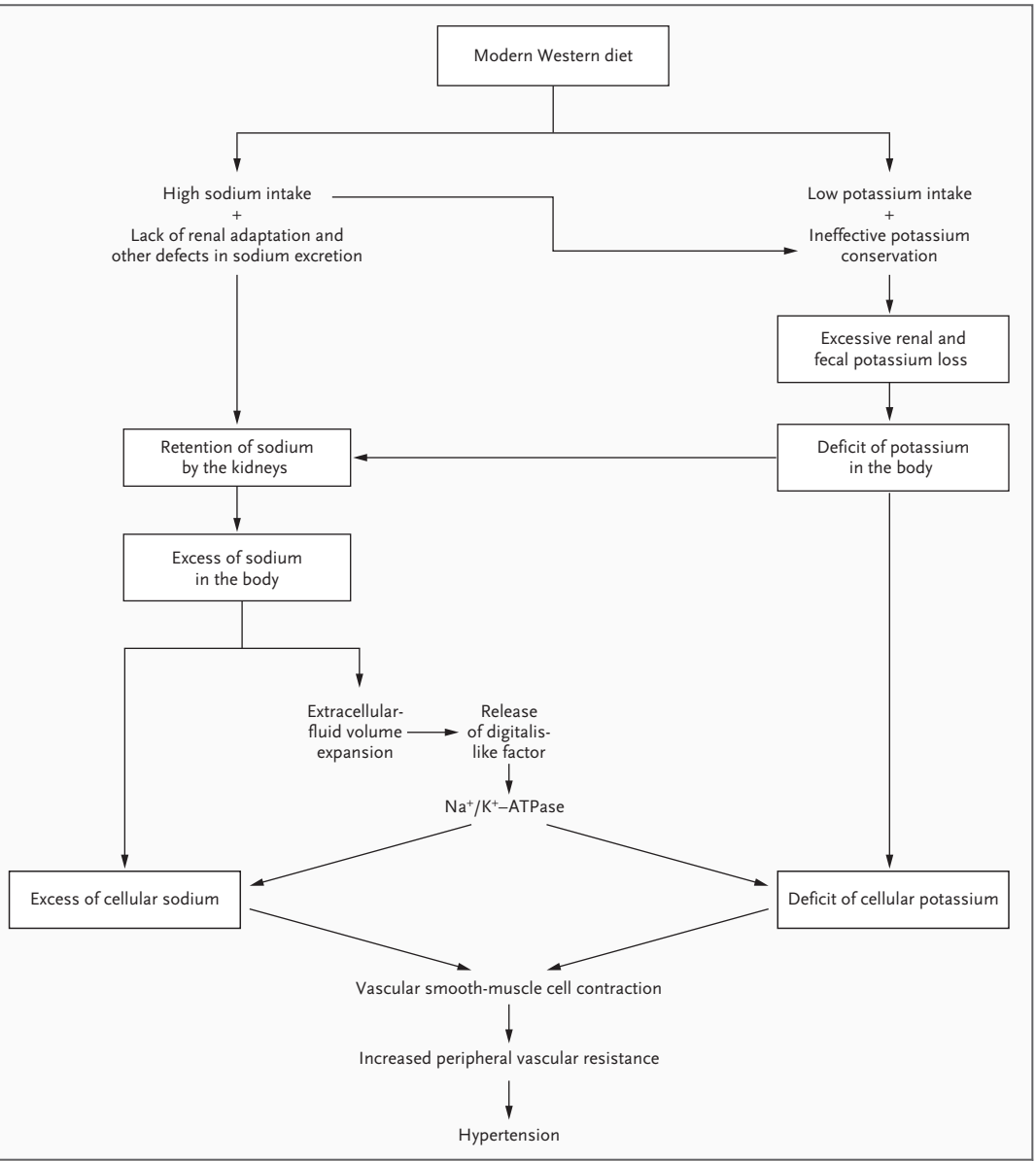

Figure 1. Interaction of the Modern Western Diet and the Kidneys in the Pathogenesis of Primary Hypertension.

The modern Western diet interacts with the kidneys to generate excess sodium and cause a deficit of potassium in the body; these changes increase peripheral vascular resistance and establish hypertension. An initial increase in the volume of extracellular fluid is countered by pressure natriuresis.

Aldosterone contributes to the retention of sodium by the kidneys. Evidence from the Framingham Offspring Study suggests that relative aldosterone excess, as defined by the higher aldosterone values within the physiologic range, predisposes normotensive subjects to hypertension.[35] In animals and humans, a low-potassium diet itself causes renal sodium retention by means of several mechanisms.[10,24,25,36]

A low-potassium diet leads to a potassium deficit in the body as a result of inadequate conservation of potassium by the kidneys and the alimentary tract; with such a diet, fecal potassium losses can exceed even urinary losses.[37] Furthermore, a high-sodium intake increases kaliuresis, especially when sodium reabsorption by the renal cortical collecting tubule (where sodium reabsorption and potassium secretion are func-

tionally linked) is enhanced (as it is in primary hypertension).[38]

Excess sodium and a deficit of potassium in hypertensive animals and humans have been described previously.[3] Exchangeable sodium (measured by the isotope-dilution technique) is increased in hypertensive subjects[39] and correlates positively with arterial pressure; this correlation is highest in older patients.[40] Despite an excess of sodium, extracellular fluid volume, plasma volume, and blood volume are not increased in primary hypertension.[41,42] Conversely, exchangeable potassium (measured by the isotope-dilution technique) correlates negatively with arterial pressure in primary hypertension.[40] Skeletal-muscle potassium is decreased in untreated hypertension, but serum potassium, generally an unreliable index of potassium content in the body, is within the normal range.[43] Systolic and diastolic blood pressures are negatively correlated with muscle potassium in normotensive and hypertensive subjects.[44]

MECHANISMS OF ALTERED SODIUM AND POTASSIUM HOMEOSTASIS

Reabsorption of filtered sodium by the renal tubules is increased in primary hypertension because of stimulation of several sodium transporters located at the luminal membrane, as well as the sodium pump, which is localized to the basolateral membrane and provides the energy for such transport (Fig. 2). A pivotal luminal transporter is sodium–hydrogen exchanger type 3, which resides in the proximal tubule and the thick ascending limb of the loop of Henle, where the bulk of filtered sodium is reabsorbed. The activity of this exchanger is increased in the kidneys of rats with hypertension.[45] Moreover, potassium depletion enhances sodium–hydrogen exchanger type 3 by inducing intracellular acidosis and by stimulating the sympathetic nervous system and the renin–angiotensin system.[46] Dietary potassium supplementation has opposite effects. The sodium–chloride cotransporter in the distal tubule, the epithelial sodium channel in the collecting duct, and the sodium pump are activated by the aldosterone excess in primary hypertension, thereby promoting sodium retention and potassium loss.[35,45] A high-sodium diet increases potassium excretion by increasing distal sodium delivery.

An endogenous "digitalis-like factor," which is identical to ouabain or a stereoisomer of ouabain, is released by the adrenal glands and the brain in response to a high-sodium diet. There are high levels of digitalis-like factor in the plasma of approximately 40% of untreated patients with primary hypertension, and these levels correlate directly with blood pressure.[47] Digitalis-like factor mediates sodium retention by increasing the activity and expression of the renal sodium pump (Fig. 2).[48]

Contrary to its short-term effects, the long-term effect of potassium depletion is to stimulate the activity and expression of the renal sodium pump, thereby promoting sodium retention.[48-50] Such stimulation has been shown in cultured renal cells (after a 24-hour incubation in a low-potassium bath) and in rats fed a low-potassium diet for 5 weeks.[49,51] This effect is similar to the response to prolonged incubation of renal cells with ouabain for 5 days or to infusion of ouabain into rats for 3 to 4 weeks; the latter maneuver raises blood pressure.[52] The long-term stimulatory effect on the renal sodium pump (which mediates sodium retention) contrasts with the inhibitory effect of potassium depletion and digitalis-like factor on the vascular sodium pump.

Additional mechanisms of sodium retention in primary hypertension have been proposed, including a congenital reduction in the number of nephrons, diminished renal medullary blood flow, and subtle acquired renal injury due to ischemia or interstitial inflammation.[3,5,7,53] It is likely that heredity contributes to primary hypertension through several genes involved in the regulation of vascular tone and the reabsorption of sodium by the kidneys.[54] Such a polygenic effect could result from gain-of-function mutations and polymorphisms in genes encoding components or regulatory molecules of the renin–angiotensin system and renal sodium transporters in subgroups of the population (Fig. 2).[45] Examples are activating polymorphisms in the genes encoding G protein–coupled receptor kinases (which regulate dopamine receptors involved in sodium reabsorption in the renal proximal tubule) and α-adducin (a cytoskeletal protein modulating the activity of the renal sodium pump).[45] Population-based investigations of candidate genes for hypertension have not produced unequivocal results, however. Expression of hypertension-related genes might be strongly affected by environmental and

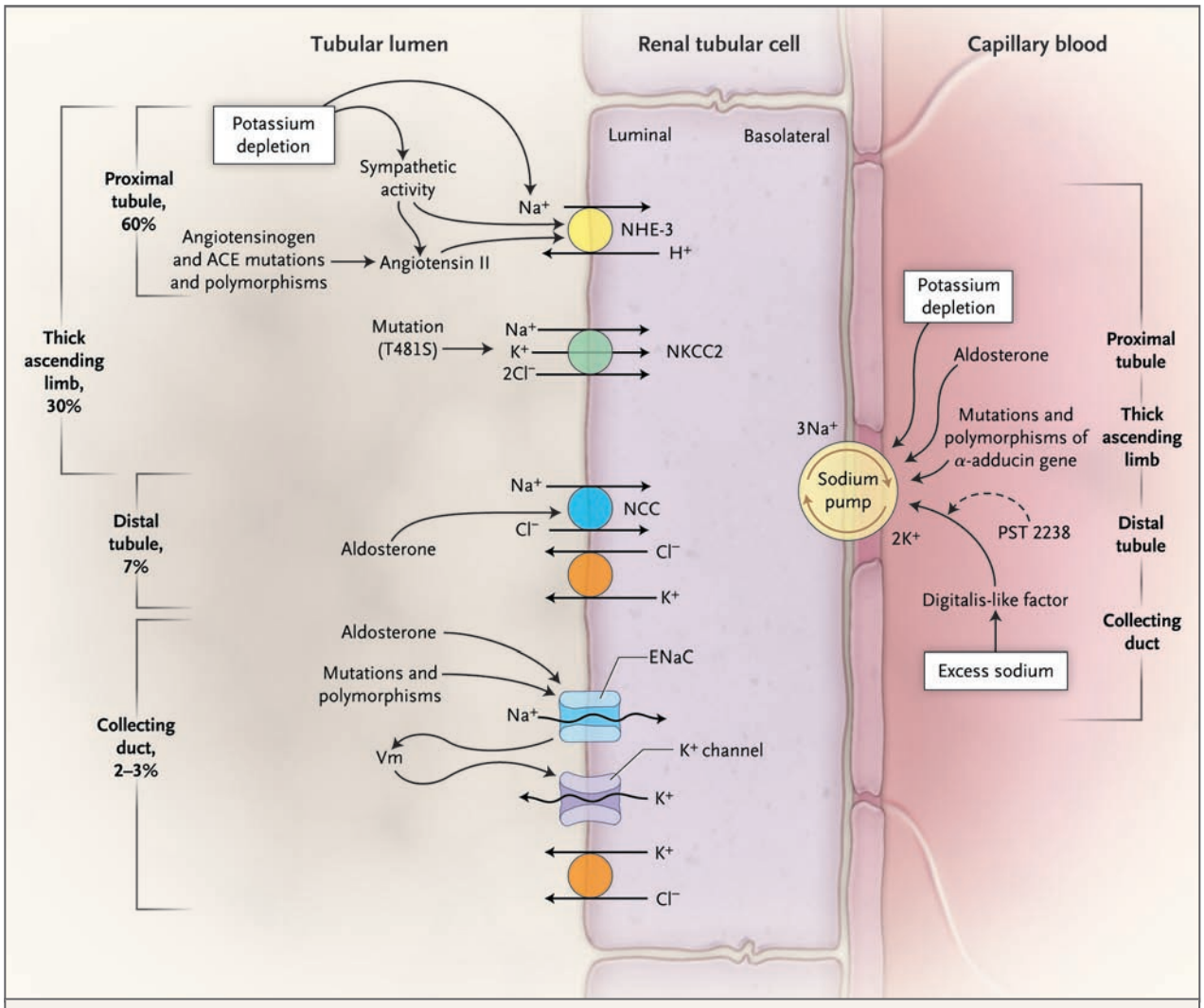

Figure 2. Molecular Mechanisms Implicated in the Retention of Sodium and Loss of Potassium by the Kidneys in Primary Hypertension.

Solid arrows indicate an increase or stimulation, and the broken arrow indicates inhibition. Numbers on the left denote the approximate percentage of reabsorption of filtered sodium in each nephronal segment during normal conditions. Several influences acting on the luminal sodium transporters and the basolateral sodium pump stimulate sodium retention and potassium loss. Promotion of sodium reabsorption by the activated epithelial sodium channel (ENaC) generates a more negative luminal membrane voltage (Vm) in the collecting duct that enhances potassium secretion through the luminal potassium channel and promotes kaliuresis. NHE-3 denotes sodium–hydrogen exchanger type 3, ACE angiotensin-converting enzyme, NKCC2 sodium–potassium2 chloride cotransporter, and NCC sodium–chloride cotransporter. PST 2238 (rostafuroxin) antagonizes the effect of digitalis-like factor on the sodium pump.

behavioral interactions that differ within a population and across populations.[55]

In rats, coadministration of sodium and mineralocorticoids results in sodium retention, potassium depletion, hypertension, and extensive tissue damage. These changes bear a remarkable similarity to the changes in rats with hypertension induced by a high-sodium and low-potassium diet, which suppresses endogenous mineralocorticoids[56,57] (Table 1). In both settings, the consequences of an excess of sodium and a potassium deficit in the body could be largely responsible for the hypertension and associated tissue injury.[58] Furthermore, in primary aldosteronism, potassium administration augments aldosterone levels and yet reduces blood pressure, normalizes the circulatory reflexes of increased sympathetic activity, and corrects baroreceptor hyporesponsiveness.[59-61]

Table 1. Effects of Mineralocorticoids plus a High-Sodium Diet or a High-Sodium and Low-Potassium Diet Alone in Laboratory Animals.*

Kidneys
Sodium retention
Potassium deficit
Potentiation of the pressor response to angiotensin II
Glomerulosclerosis, tubulointerstitial disease
Heart
Myocardial ischemia, necrosis, fibrosis, hypertrophy, failure
Arteries
Hypertension
Hypertrophy of smooth muscle
Fibrinoid necrosis of the media
Perivascular-cell infiltration
Endothelial dysfunction
Reduction in vascular compliance
Atherogenic action
Central nervous system
Autonomic imbalance
Stimulation of sympathetic outflow
Depressed baroreceptor sensitivity
Stroke
Metabolism and other effects
Insulin resistance, glucose intolerance
Stimulation of the formation of reactive oxygen species
Stimulation of the synthesis of transforming growth factor β
Adverse action on fibrinolysis

* The rate of secretion of endogenous mineralocorticoids decreases in animals ingesting a high-sodium and low-potassium diet through a suppressive effect of the high-sodium intake on the renin–angiotensin system and the direct action of hypokalemia on the adrenal cortex. Therefore, in both settings, the consequences of an excess of sodium and a potassium deficit in the body might be largely responsible for hypertension and tissue damage.

SODIUM RETENTION, POTASSIUM DEPLETION, AND HYPERTENSION

EFFECTS ON THE ARTERIAL WALL

Sodium retention, by means of the release of digitalis-like factor, and a potassium deficit or hypokalemia inhibit the sodium pump of arterial and arteriolar vascular smooth-muscle cells, thereby increasing the sodium concentration and decreasing the potassium concentration in the intracellular fluid[47,62] (Fig. 3). Increased intracellular sodium stimulates the sodium–calcium exchanger type 1 in the membrane, driving calcium into cells. A deficit of potassium in the body or hypokalemia inhibits potassium channels in the cell membrane, depolarizing the membrane (the membrane potential shifts closer to 0). Because of its electrogenic nature, the inhibition of the sodium pump itself decreases the membrane potential. Membrane depolarization in the vascular smooth-muscle cells promotes a further rise in intracellular calcium by activating voltage-dependent calcium channels in the membrane, calcium channels in the sarcoplasmic reticulum, and the sodium–calcium exchanger.[63] The increased cytosolic calcium caused by these mechanisms triggers contraction of the vascular smooth muscle. PST 2238 (rostafuroxin), a compound that antagonizes the effects of digitalis-like factor on both the vascular and renal sodium pump, and SEA 0400, a specific inhibitor of sodium–calcium exchanger type 1, have shown promise as new antihypertensive agents, validating the importance of digitalis-like factor and sodium–calcium exchanger type 1 in primary hypertension.[7,48]

The homeostasis of sodium and potassium plays an important role in endothelium-dependent vasodilatation, which is defective in primary hypertension.[64] Sodium retention decreases the synthesis of nitric oxide, an arteriolar vasodilator elaborated by endothelial cells, and increases the plasma level of asymmetric dimethyl L-arginine, an endogenous inhibitor of nitric oxide production.[65] Sodium restriction has the opposite effects. A high-potassium diet and increases in serum potassium, even within the physiologic range, cause endothelium-dependent vasodilatation by hyperpolarizing the endothelial cell through stimulation of the sodium pump and opening potassium channels[66,67] (Fig. 4). Endothelial hyperpolarization is transmitted to the vascular smooth-muscle cells, resulting in decreased cytosolic calcium, which in turn promotes vasodilatation. Experimental potassium depletion inhibits endothelium-dependent vasodilatation.[66]

The contributions of prostaglandins, endothelin, atrial natriuretic peptides, kallikrein, and eicosanoids, as well as alterations in calcium balance, to potassium-induced changes in arterial and arteriolar tone and blood pressure are not well defined.[68-71] Experimental studies suggest that in addition to its effects on vascular tone, a potassium-rich diet decreases cardiovascular risk by inhibiting arterial thrombosis, atherosclerosis, and medial hypertrophy of the arterial wall.[72-74]

The long-term antihypertensive effect of low-dose thiazide diuretics reflects not hypovolemia but mainly decreased systemic vascular resistance,

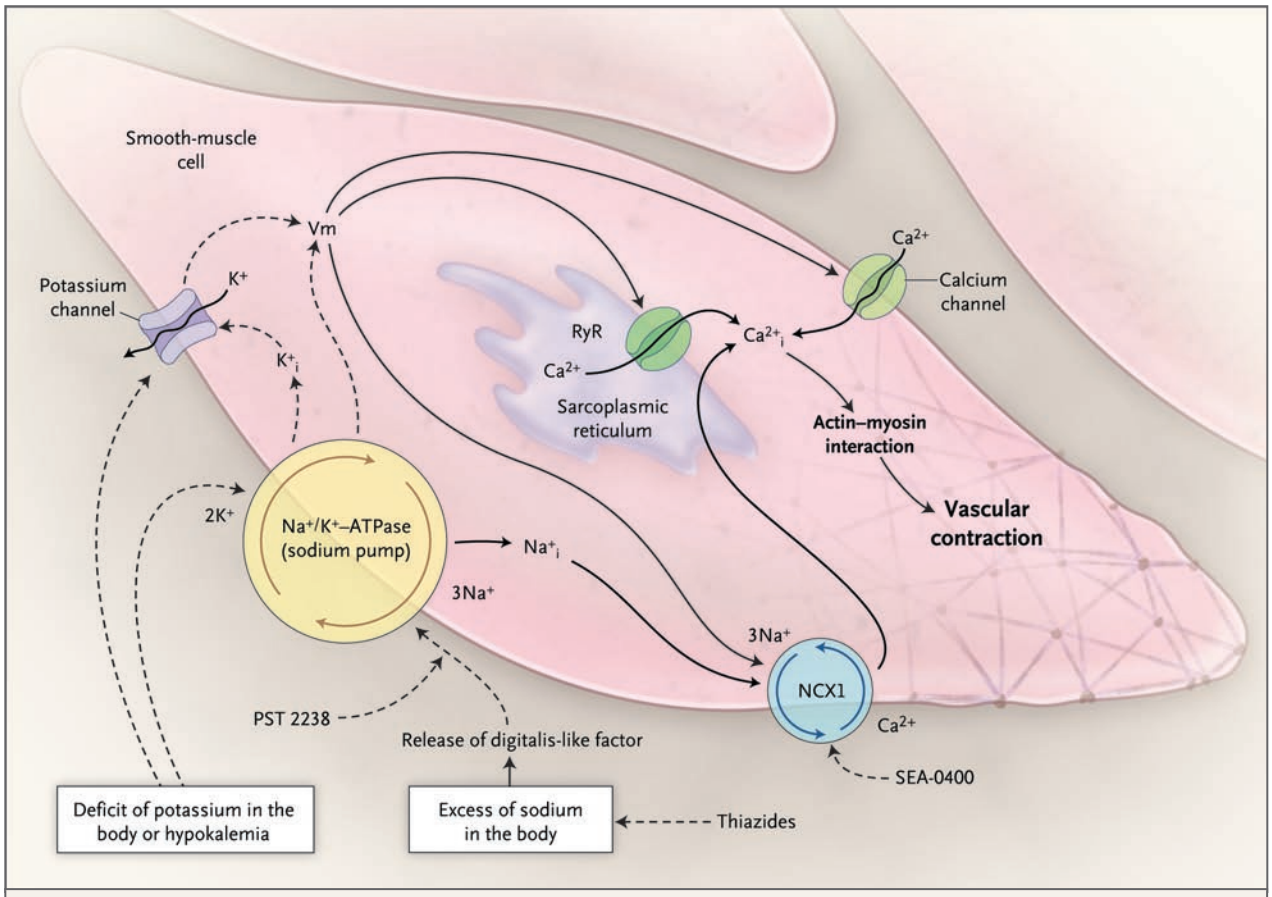

Figure 3. Molecular Pathways Implicated in the Generation of Increased Arterial and Arteriolar Smooth-Muscle Tone by an Excess of Sodium and a Deficit of Potassium in Primary Hypertension.

Solid arrows indicate an increase or stimulation, and broken arrows indicate a decrease or inhibition. The inhibition of the sodium pump and the resulting stimulation of the sodium–calcium exchanger type 1 (NCX1) increase the intracellular concentration of calcium that in turn triggers actin–myosin interaction and stimulation of vascular contraction. Na^+_i denotes intracellular sodium concentration, K^+_i intracellular potassium concentration, Ca^{2+}_i intracellular calcium concentration, Vm membrane potential, and RyR ryanodine-receptor calcium channel. PST 2238 (rostafuroxin) antagonizes the effect of digitalis-like factor on the sodium pump. SEA-0400 is a specific inhibitor of the bidirectional NCX1 preferentially blocking the calcium influx pathway.

probably caused by changes in the ionic composition of the vascular wall.[7,75] Natriuresis triggers cellular sodium loss and the redistribution of potassium into cells.[76] The activation of potassium channels contributes to thiazide-induced vasodilatation.[77]

EFFECTS ON THE BRAIN

Changes in the concentrations of sodium and potassium in the cerebrospinal fluid, acting on a sensing region of the brain probably located near the third ventricle, have substantial but obverse effects on blood pressure (Fig. 5).[45,78-82] Increasing the concentration of sodium in the cerebrospinal fluid by the intraventricular administration of hypertonic saline raises blood pressure, whereas increasing the concentration of potassium in the cerebrospinal fluid by administering potassium chloride has the opposite effect.[45,78] Increasing dietary sodium chloride in animals and humans elicits small but significant increases in serum sodium[83,84]; limited data suggest that the resulting increases in the concentration of sodium in the cerebrospinal fluid contribute to an elevation in blood pressure.[45,84]

The intraventricular infusion of aldosterone at a dose that is too small to raise blood pressure when infused systemically decreases potassium

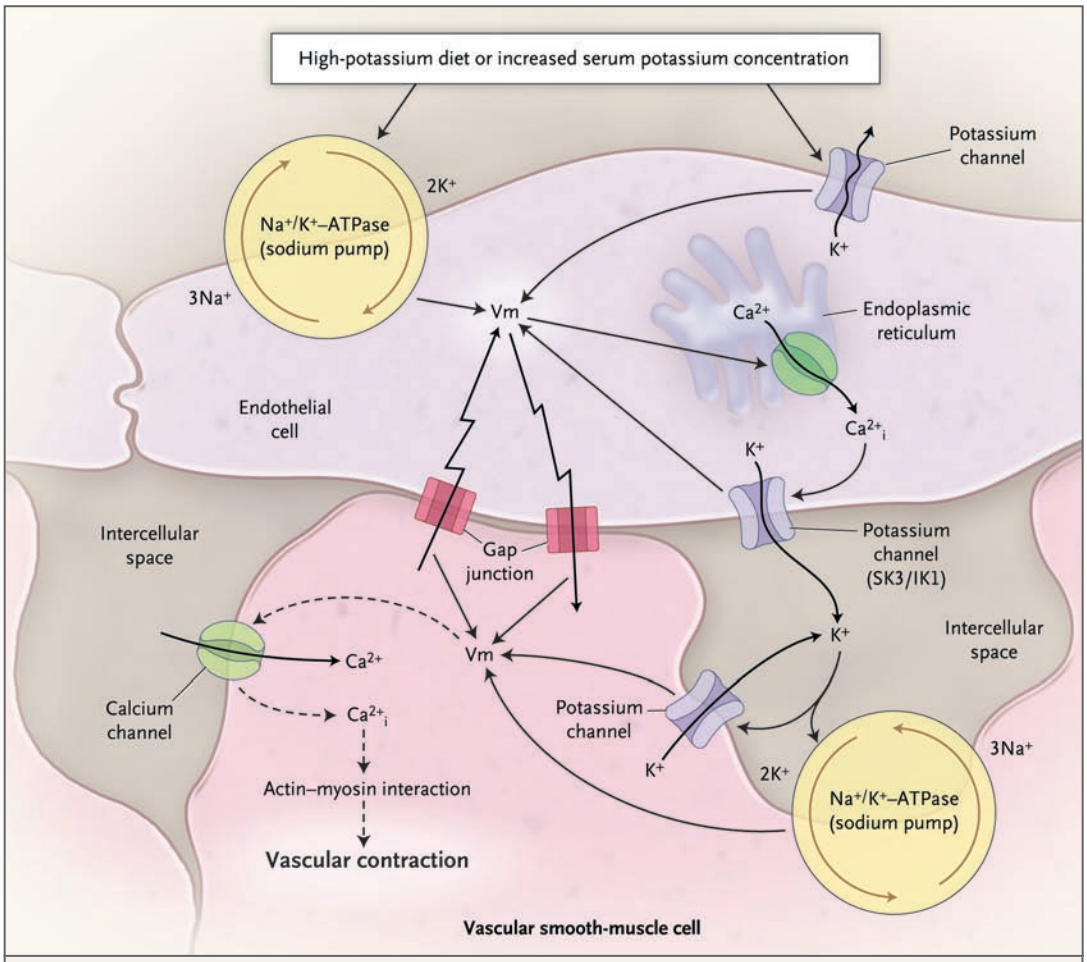

Figure 4. Molecular Pathways Implicated in Potassium-Induced, Endothelium-Dependent Vasodilatation.

Solid arrows indicate an increase or stimulation, and broken arrows indicate a decrease or inhibition. The stimulation of the sodium pump and the opening of the potassium channels hyperpolarize the endothelial cell (with membrane potential [Vm] shifting to more negative values). Endothelial-cell hyperpolarization is transmitted to the vascular smooth-muscle cell by means of myoendothelial gap junctions and also by increasing the intracellular calcium concentration (Ca^{2+}_i). The latter change activates potassium channels of small (SK3) and intermediate (IK1) conductance localized to the cell membrane, causing the potassium to exit the cells and to accumulate in the myoendothelial intercellular space. This accumulation of potassium adds to vascular smooth-muscle hyperpolarization by activating membrane potassium channels and stimulating the sodium pump. Vascular smooth-muscle hyperpolarization lowers Ca^{2+}_i, resulting in vascular relaxation.

in the cerebrospinal fluid and causes hypertension. The administration of either potassium or prorenone, a mineralocorticoid antagonist, through the same route prevents the decrease in potassium in the cerebrospinal fluid and the pressor effect of aldosterone (Fig. 5).[80,81] The salutary action of small doses of spironolactone or eplerenone in hypertension and heart failure may largely depend on the central effects of the drugs in preventing or minimizing a reduction in the extracellular potassium in the brain, thereby moderating sympathetic discharge.[85]

The central actions of changes in the concentrations of sodium and potassium in the cerebrospinal fluid and of an excess of sodium and a deficit of potassium in the body are probably mediated by changes in the activity of the neuronal sodium pump and the renin–angiotensin system in the brain.[45,78,82] These changes alter sympathetic outflow, which then causes direc-

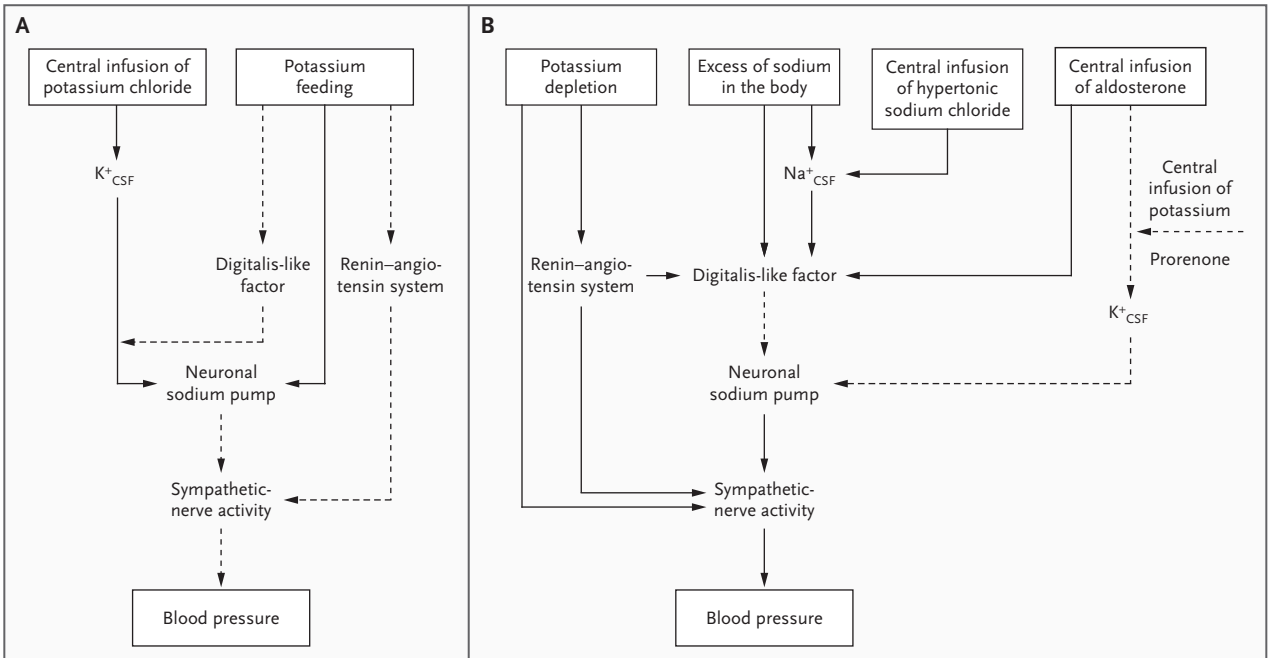

Figure 5. Molecular Pathways Implicated in the Central Effects of Sodium and Potassium on Blood Pressure.

Solid arrows indicate an increase or stimulation, and broken arrows indicate a decrease or inhibition. Panel A depicts the central effects of intracerebroventricular infusion of potassium chloride or of potassium feeding on the blood pressure of normotensive rats. Long-term intracerebroventricular infusion of potassium chloride prevents the development of deoxycorticosterone–salt hypertension. Panel B depicts the central effects of potassium depletion and sodium excess in the body, or of the intracerebroventricular infusion of hypertonic sodium chloride or aldosterone on the blood pressure of normotensive rats. K^+_{CSF} denotes potassium concentration in the cerebrospinal fluid and Na^+_{CSF} sodium concentration in the cerebrospinal fluid. Prorenone is an aldosterone antagonist.

tional changes in blood pressure.[86,87] Baroreceptor sensitivity is depressed by potassium depletion and restored by potassium supplementation.[59]

EFFECTS ON METABOLISM

Potassium depletion inhibits insulin secretion and is associated with glucose intolerance, whereas potassium infusion and hyperkalemia increase the secretory rate of insulin by changing the membrane potential of pancreatic beta cells.[88,89] Insulin triggers endothelium-dependent vasodilatation in skeletal muscle by causing the release of nitric oxide[90]; this response is impaired in primary hypertension.[91]

Thiazide-induced hypokalemia worsens glucose intolerance in type 2 diabetes mellitus and increases the risk of the disorder; correction of hypokalemia ameliorates the glucose intolerance.[92] As compared with diuretics, angiotensin-converting–enzyme inhibitors and angiotensin II receptor blockers, which promote potassium retention, are associated with a lower risk of new-onset type 2 diabetes.[93] Treatment of thiazide-induced hypokalemia with potassium augments the antihypertensive effect of the diuretic.[94]

IMPLICATIONS FOR PREVENTION AND TREATMENT

A modified diet that approaches the high potassium:sodium ratio of the diets of human ancestors is a critical strategy for the primary prevention and treatment of hypertension. Weight loss with diets rich in fruits and vegetables has been attributed both to the low caloric density and to the high potassium content of these diets, which tend to increase the metabolic rate.[95]

In its 2002 advisory, the coordinating committee of the National High Blood Pressure Education Program identified both a reduction in dietary sodium and potassium supplementation as proven approaches for preventing and treating hypertension.[96] The Institute of Medicine recommends an intake of sodium of 65 mmol per day

(approximately 3.8 g of sodium chloride per day) for adults 50 years of age or younger, 55 mmol per day (approximately 3.2 g of sodium chloride per day) for adults 51 to 70 years of age, and 50 mmol per day (approximately 2.9 g of sodium chloride per day) for those 71 years of age or older. The institute also advises adults to consume at least 120 mmol of potassium per day (approximately 4.7 g of potassium per day, which is about twice the current U.S. average).[10] These targets would require modifications for special groups, including competitive athletes, persons working in hot environments, patients with chronic kidney disease or diabetes, and persons taking medications that affect potassium balance. Adoption of the institute's recommendations would increase the dietary potassium:sodium ratio by a factor of 10, from approximately 0.2 to approximately 2.0, which is much closer to our ancestral standard.

The concern that sodium restriction might increase cardiovascular risk by activating the sympathetic and renin–angiotensin system and by adversely affecting blood lipids and insulin sensitivity appears to be groundless for the recommended sodium intake.[10] Forms of potassium that do not contain chloride, such as those found naturally in fruits, vegetables, and other foods, offer larger cellular entry in exchange for sodium and greater antihypertensive effects.[10,97]

Following these recommendations would require a comprehensive, culture-sensitive campaign targeting both the general public and health care professionals. Food processing drastically changes the cationic content of natural foods, increasing sodium and decreasing potassium. Only approximately 12% of dietary sodium chloride originates naturally in foods, whereas approximately 80% is the result of food processing, the remainder being discretionary (added during cooking or at the table).[98] Apart from educating the public, an agreement by the food industry to limit the deviation of the cationic content of processed foods from their natural counterparts is essential.

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