Role of Dietary Potassium in the Treatment of Hypertension

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SUMMARY This review summarizes the historical development and recent resurgence of interest in dietary potassium as a factor in hypertension. Some epidemiologic evidence has suggested that potassium intake by humans may be inversely related to the level of arterial blood pressure. Other studies have suggested that a marked reduction in the Na⁺/K⁺ ratio of the human diet reduces the blood pressure of normotensives. Further, the administration of high potassium diets has resulted in a lowering of blood pressure in some animal models of hypertension. Several possible mechanisms for this putative antihypertensive effect are evident. Some observations suggest that potassium could act as a diuretic agent and thereby reduce extracellular fluid volume, which in turn could result in decreased blood pressure. An alternative mechanism of action is that potassium may alter the activity of the renin-angiotensin system and reduce angiotensin influences on vascular, adrenal, or renal receptors. Other evidence supports the possibility that potassium modifies central or the peripheral neural mechanisms that regulate blood pressure. In addition, high potassium diets could reduce blood pressure by relaxing vascular smooth muscle and reducing peripheral vascular resistance directly. Although diets high in potassium content do appear to modify arterial blood pressure under some circumstances, particularly in salt-dependent hypertension, a high potassium intake has not always attenuated blood pressure in all models examined. Further, evaluation of these data do not allow definite conclusions regarding a common mechanism through which potassium exerts these effects. (Hypertension 5: 864-872, 1983)

KEY WORDS • hypertension • potassium • diuresis • renin-angiotensin • aldosterone • natriuresis

THESE article reviews the evidence that a balance between dietary sodium and potassium intake is important in the regulation of blood pressure. However, at the outset it should be noted that the role of dietary sodium in the initiation and maintenance of idiopathic or essential hypertension remains controversial. One theoretical argument for the importance of an excessive intake of salt (or a defective ability of the kidney to excrete salt) in hypertension is that it increases extracellular fluid volume, plasma volume, and cardiac output. This increases arterial pressure through an adaptive increase in (long-term, whole body autoregulation) peripheral resistance. The increased peripheral resistance maintains the arterial pressure as the cardiac output returns to normal. A parallel hypothesis suggests that excess salt intake increases peripheral resistance directly. These hypotheses have been discussed in detail in recent publications.1-4

Although the contention that manipulations of sodium intake over the normal dietary range of 140 to 260 mmoles/day affects blood pressure acutely remains controversial, it seems better accepted that chronically altered Na⁺ intake may be causal in long-term blood pressure control, especially in the subgroup of the population that is genetically predisposed to develop essential hypertension.3 A corollary of this hypothesis is that the subsection of the population with a genetic predisposition for essential hypertension would not become hypertensive in the absence of exposure to diets of high salt content. Further, the increased level of blood pressure observed in these individuals can often be correlated directly with increased levels of sodium intake.2,4

One alternative hypothesis proposes that it is not sodium intake per se but the ratio of sodium to potassium that is the important factor in hypertension. This concept was elaborated in detail by Meney and Ball5 in 1958 and was based on their observations that animals fed toxic amounts of sodium chloride survived.
longer if fed increased amounts of KCl contemporaneously with NaCl. Although they did report that the added potassium prevented the increase of total body sodium that was observed in the groups treated with high salt diets alone; their results were confused by the lack of correlation of blood pressure reduction to prolonged survival in some of the potassium-treated groups. The rationale for their study was based on the belief that the natural diet of humans is high in potassium and low in sodium, in contrast to the reversal of this ratio in the human diet today. They suggested that the increase of the dietary sodium/potassium of contemporary diets was the result of factors such as the cooking of food with coincident leaching of potassium salts, extensive use of sodium salts as a food preservative, and the increased availability and habitual use of sodium chloride as a condiment.

Since it is currently established that mild hypertension should be treated, many people need long-term therapy to achieve adequate blood pressure control. Thus, the idea that dietary manipulation of sodium vs potassium intake could influence the development of hypertension or reduce established hypertension is especially appealing and has resulted in a resurgence of interest in the potential antihypertensive effects of an increased dietary intake of potassium.

**Epidemiological Studies**

Several investigators have tested the hypothesis that high potassium diets have antihypertensive effects by examining correlations between blood pressure and urinary potassium excretion or by correlating blood pressure and urinary sodium/potassium ratios. These studies assume that urinary excretion ratios of electrolytes accurately reflect dietary intake. However, it is known that spot urine excretion data for sodium do not accurately reflect steady-state dietary electrolyte intake. This circumstance could jeopardize conclusions based on such “spot” urine data in some studies where urinary excretion data are less complete.

Some of the many studies examining the role of potassium in the regulation of blood pressure have come from Japan. The traditional diet of the Japanese is high in salt (up to 400 mmoles/day in some regions) and this is thought to be causal in the higher mortality from stroke observed in Japan compared to that of Western cultures. In a large epidemiological study of a population from Shimano prefecture where the traditional lifestyle and diet were preserved, blood pressure was inversely correlated with urinary potassium excretion and positively correlated with the urinary Na⁺/K⁺ ratio, especially in the older age groups. A similar relationship was found when two neighboring regions with markedly different prevalences of hypertension were compared. Individuals from the region with the lower prevalence of hypertension had higher urinary potassium excretions, presumably because of increased consumption of potassium in the form of apples, since the area studied is a region of major apple production.

Surveys of mixed groups of hypertensive and normotensive Americans have also revealed a negative correlation between blood pressure and urinary potassium excretion or urinary Na⁺/K⁺ ratios. A similar relationship was found in the normotensive subgroup of a study performed in Sweden, where, based on blood pressures, individuals were assigned to one of three groups designated as normotensive, borderline hypertensive, and hypertensive. However, the negative correlation of blood pressure and urinary potassium excretion and the positive correlation of blood pressure and the urinary Na⁺/K⁺ ratio, which were significant in the normotensive group, were not found when all three groups of the population were examined as a single unit. As noted by others, the correlation of data for an entire population may mask a real effect in a subset that is sensitive to the intervention. In this case, the effect may be masked in the hypertensive subset of patients which is the group of major interest.

Other investigators have attempted to correlate blood pressure with plasma potassium concentration. Since the regulation of plasma potassium is under complex homeostatic control, and then only roughly reflects total body potassium content, it is not valid to assume that it reflects dietary potassium intake or total body K⁺ accurately. However, plasma potassium concentration rather than total body potassium content may be of greater significance in the epidemiology of hypertension in that this parameter directly contributes to gradients for potassium across the cell and resting membrane potentials or potentials necessary to evoke depolarization of excitable tissues, including vascular smooth muscle.

Serum potassium concentration and blood pressure have been found to be negatively correlated in men in their 4th decade of life from six provinces in Japan. A similar negative correlation was observed when serum potassium levels and blood pressure were determined in a group of hypertensives and normotensives in Scotland. The latter study also reported negative correlations between blood pressure and exchangeable and total body potassium, and positive correlations between blood pressure and exchangeable and total body sodium. In both of these studies, drugs, particularly diuretics, were excluded as a possible source of artifact that could have comprised the validity of the observations.

Several other studies have been unsuccessful in documenting a relationship between blood pressure levels and dietary potassium intake. In a subset of the Framingham population, no correlation of blood pressure levels with dietary salt preference could be established. Further, in an attempt to eliminate the errors implicit in extrapolating dietary histories to true sodium intake, blood pressure was correlated with measured 24-hour urine Na⁺ excretion, K⁺ excretion, and Na⁺/K⁺ urinary ratios for a subgroup of 297 individuals of the Framingham study group, and, again, no significant relationship could be established. The range of sodium excretion with which these blood pressure data were correlated was from approximately...
40 to 200 mM/day and the (molar) Na⁺/K⁺ ratio ranged from approximately 1 to 4.15 Twenty-four-hour K⁺ excretions were observed to range from approximately 25 to 200 mM for the same patients.15 Since these data did not include a group exhibiting sodium excretion rates at the lower end of the dietary range (<40–50 mEq Na⁺/24 hrs), failure to document a relationship might have been compromised.15

A careful study of both dietary sodium and potassium intake and urinary electrolyte excretion from a random sample in Evans County, Georgia, also failed to reveal a significant relationship between potassium and sodium intakes and the level of blood pressure.16 However, lower urinary potassium excretion and dietary intake were observed in the black subset, and the authors suggested that this might be a factor contributing to the higher prevalence of hypertension in this group.16 Other investigators reported lower K⁺ excretion for black children compared to white children in Louisiana17 and Mississippi,11 although K⁺ excretion alone was not correlated with blood pressure in either survey.11,17

**Dietary Intervention Studies in Humans**

Another approach used to test the putative anti-hypertensive effect of potassium has been to reduce the dietary sodium/potassium ratio and evaluate the effects on blood pressure. This approach has been applied to studies of both human and experimental hypertension. Some of these data should be interpreted with caution, since they may have excluded the hypertensive subgroup of the population, the group that might be of most interest by virtue of their susceptibility to sodium excess or potassium deficiency. Such studies might be compromised further by the relatively short period of study. For instance, it could be that the chronic dietary background of high salt intakes precludes the ability to detect the effect of short-term alterations in Na⁺ or K⁺ levels in the diet.

The earliest studies of this type were made by Addison14 in 1928 who placed a group of five hypertensives including himself on a low salt diet and supplemented this diet with either sodium salts or potassium salts. Blood pressure increased within a few hours when sodium salts were ingested but decreased when potassium salts were taken. Addison took advantage of these observations on the effects of potassium salts to treat patients with hypertension. Apart from the reduction in blood pressure levels, he reported associated subjective feelings of well-being by the patients. Addison believed that the efficacy of the potassium salts was caused by the natriuresis they induced, although he did not investigate this possibility.

McQuarrie also became interested in the effects of K⁺ in the control of blood pressure when he studied a 15-year-old diabetic with an abnormal craving for salt, resulting in NaCl intakes as high as 1550 mmoles per day. He found that if large amounts of potassium were added to the diet of this patient, blood pressure was reduced to lower levels. He evaluated this observation further by examining other juvenile diabetics and observed that blood pressure increased when 600–700 mmoles/day of NaCl were added to the diet. The addition of 200 mmoles/day of KCl attenuated the blood pressure increases consequent to high salt diets.19

Priddle,20 who gave a low sodium, high potassium diet to a group of 45 hypertensives, including some with impaired renal function, reported a lowering of blood pressure and an improvement in their general medical condition. The rice-fruit diet utilized by Kempner for treatment of hypertension resulted in consistent reductions of blood pressure.21 This diet markedly reduced levels of Na⁺ intake and the Na⁺/K⁺ diet ratio by 99%.21 However, the reductions in blood pressure in these studies21 were confounded by other variables, such as weight loss and other metabolic sequelae of negative calorie balance.

These studies were followed by a period of relative inactivity in the study or use of potassium as an antihypertensive agent. However, recently there has been a resurgence of interest in the possible antihypertensive properties of increased dietary intake of potassium and the potential mechanisms responsible for these effects. Luft et al.,22 investigated the effects of increased sodium chloride intake on the blood pressure of normotensive subjects. The administration of amounts of sodium chloride (up to 1500 mmoles/day) produced a small rise in blood pressure in these initially normotensive men that was associated with a marked kaliuresis. If the potassium deficit resulting from Na⁺ loading was prevented by supplemental KCl, the increase of blood pressure was attenuated.23

In a different study, resting blood pressure was reduced when a group of 21 normotensive young adults consumed a low sodium, high potassium diet but was unaffected by diets high in sodium or high in potassium content when administered separately.25 Another investigation of a decreased dietary sodium-to-potassium ratio did not report detectable changes in blood pressure in patients with mild hypertension.24 Since only minor changes of salt or potassium intake can result from using condiments of altered Na/K composition or reduced discretionary salt intake, it is not surprising that two studies that tested the effects of replacing table salt with a 50:50 mixture of NaCl and KCl in normotensive patients failed to find any change in blood pressure.25,26 Also, dietary supplements of either sodium chloride or potassium chloride given to normotensives on an otherwise normal diet did not change blood pressure.25,26

Two recent studies have assessed the effect of approximately doubling of normal potassium intake (from approximately 60 or 75 mM/day to 120 or 160 mM/day, respectively) on blood pressure in essential hypertensives who maintained normal intakes of sodium during the period of K⁺ supplementation.27,28 Both studies reported significant reductions of arterial pressure of 10%27 and 4%,29 which were insufficient to normalize blood pressure in these hypertensive patients.27,28

The inconsistency of the results reported by many investigators based on different or even similar experi-
mental approaches emphasizes the difficulties of reaching definitive conclusions from such studies. However, it is possible that the fall of blood pressure secondary to a reduction of the molar Na+/K+ ratio in the diet is a dose-related phenomenon. The studies of increased potassium intake that were associated with a fall in blood pressure resulted from a reduction of the molar urinary Na+/K+ ratio from the normal level of 2.96 down to 0.62 (a 79% reduction of molar ratios) whereas those that were ineffective generally reduced the molar Na+/K+ ratio by lesser magnitudes (from 1.7 to 0.7, a 59% reduction of molar ratios) or to higher minimum molar ratios (from 5.8 to 2.2, a 62% reduction of molar ratio). Although both epidemiological observations and studies in humans where dietary interventions have been used to alter potassium intake suggest that potassium may be important in the control of blood pressure, the evidence at the present time is far from conclusive.

Dietary Intervention Studies in Animals

Many dietary intervention studies in animals have utilized models of hypertension that develop elevated blood pressure in response to salt loading. Meneely and coworkers examined the effects of diets with an extremely broad range of sodium chloride contents (from approximately 25 to 1600 mmoles/kg of rat diet) in Sprague Dawley rats. The simultaneous addition of large amounts of potassium (as high as 740 mmoles/kg food day) to some of the groups increased survival. However, the added potassium was associated with only subtle attenuation of hypertension in some of the treated groups, and the increased survival could not be correlated directly with reduced blood pressures. This amelioration of the toxicity of high sodium diets was associated with a reduction of the molar ratio of dietary Na+/K+ from the range of 15–20 to 2.2.

Dahl et al. studied the effects of altering the dietary Na+/K+ ratios while maintaining a high sodium intake in his salt-sensitive strain of rats. The rate of rise of blood pressure was attenuated in direct proportion with the molar ratio of Na+/K+ in the diet. This effect has been confirmed by others in additional studies using the Dahl salt-sensitive rat model of hypertension and also reported in other models of salt-induced hypertension.

The Wistar-Kyoto strain of spontaneously hypertensive rats has been reported to be protected from the pressor effect of high dietary sodium by the concurrent administration of potassium. Furthermore, in one study, the increase of blood pressure in two-kidney, one clip renal hypertensive rats consuming a diet of normal Na+ and K+ contents was attenuated if potassium was added to the drinking water. This latter study is of particular interest in that it examined the possibility that an increased potassium intake can moderate blood pressure when dietary sodium is maintained at normal levels. Our own recent experiments failed to confirm these observations when we tested the ability of three diets with varying ratios of Na+/K+ but, iden-

tical total electrolyte content (i.e., sum of K+ and Na+ contents constant) to reduce blood pressure of two-kidney, one clip Goldblatt hypertensive rats. Although the results of the study of Suzuki et al. and our own are apparently conflicting, it should be noted that the data are not comparable because the experimental design of the Suzuki study used much higher total electrolyte or solute intakes than ours.

Although antihypertensive effects of increased potassium intake may be apparent in some models of hypertension in animals other than the rat, this interpretation should be drawn with great caution. For example, increasing the potassium intake of intact, normotensive dogs from 30 to 200 mmoles per day resulted in no change in the blood pressure. However, if the animals were adrenalectomized and given replacement amounts of mineralocorticoids at a fixed dose, the blood pressure did decrease in response to high potassium intake and was associated with a marked natriuresis. Hypertension induced by administration of ACTH to sheep is typically associated with hypokalemia but replacement of the potassium deficit was reported not to affect the blood pressure.

In conclusion, some of the rat models studied appear to exhibit attenuated levels of blood pressure in response to reduction of the dietary Na+/K+ ratio. Further, the data suggest generally that a high potassium intake is effective in reducing blood pressure only in forms of hypertension where blood pressure is sensitive to variations in sodium intake.

Possible Mechanisms for the Antihypertensive Effect of Potassium

Although the previously cited evidence does not clearly establish that increased dietary potassium intake has consistent antihypertensive effects, several mechanisms have been proposed that could explain the reduction in pressure when it does occur:

1. Central or peripheral nervous system effects
2. Diuretic properties of potassium
3. Altered activity of the renin-angiotensin aldosterone axis
4. Direct alterations of peripheral resistance
5. Antagonism of the effects of natriuretic hormone.

Potassium and the Nervous System

Several lines of evidence suggest that an increased potassium intake might influence activity of the peripheral or central neural mechanisms that regulate arterial pressure.

The stage for the premise that altered K+ intake might modify neural regulation of blood pressure was set by the elegant studies of DeChamplain and coworkers. The results of these classic experiments suggested an accelerated turnover and decreased storage of norepinephrine in peripheral tissues of DOCA-salt hypertensive rats. This was detectable in prehypertensive phases and could be normalized by treatment with salt-
restricted diets. Other observations suggest a possible mechanism for the interaction of K+ with neural transmission. Isolated strips of dog and rat arteries develop contractions when exposed to potassium-free solutions. This response can be reversed by increasing the potassium concentration of the bathing solution or by application of phenolamine. There is also evidence that re-uptake of norepinephrine by sympathetic nerve terminals is influenced by the relative external concentration of Na+ and K+. However, it would seem unlikely that this mechanism contributes significantly to the control of vascular resistance in that hypokalemic vasoconstriction and hyperkalemic vasodilation persist following denervation or application of phenolamine.

The low sodium, high potassium diet, which was associated with a decrease in the resting blood pressure in humans, was also associated with an increase in baroreceptor activity. In addition, the pressor and heart rate responses to intravenous administration of norepinephrine were attenuated when patients were pretreated with high potassium diets. However, it is impossible to deduce from observations such as these whether the reduction of blood pressure is causally related to the increased dietary potassium or merely an associated phenomenon.

In conclusion, several lines of evidence both in humans and rats indicate that potassium can modify the activity of the central and peripheral nervous systems, but whether these phenomena are directly related to the possible antihypertensive effect of potassium remains to be clarified.

**Potassium as a Diuretic**

Potassium has been used as a diuretic since Thomas Willis advocated its use for the treatment of dropsy in 1679. A systematic study of the diuretic effect of potassium in eight normal subjects and 60 patients with a variety of edematous states was undertaken by Keith and Binger in 1935. With approximately 150 mmoles of potassium chloride per day, they reported a satisfactory diuresis in 80% of their patients without any evident toxic effects.

Potassium infused directly into the renal artery of a dog produced a prompt diuresis and natriuresis. The same effect was reported for rats, and is thought to be mediated by the inhibition of sodium reabsorption in the proximal tubule. Chronic studies, however, showed a less consistent effect. Although in rats the addition of potassium to the diet can result in a more sustained diuresis and natriuresis, in dogs the response appears to be transient, and overall sodium balance is restored within a few days.

There is also evidence that potassium can have a diuretic and a natriuretic effect both in hypertensive and normotensive humans. One study reported a dose-dependent natriuresis with potassium intakes of up to 300 mM per day in healthy adults on an electrolyte-free diet for a period of 4 days. Although an initial natriuresis and diuresis occurs with potassium administration, sodium balance is generally restored within the first week. Although constancy of body weight would suggest no dramatic changes in total body water or sodium content, relevant data for these factors were not reported. Supporting the natriuretic effect of potassium is the study of Meneely and co-workers in which total body sodium was documented to be decreased during treatments with various salt-potassium diet combinations in rats. It is apparent that, under some conditions, potassium can be an effective agent, chlorisodamine, to Sprague-Dawley rats on a high potassium diet. However, it is possible that altered intracellular activity of Na+ or K+, effects on Na+-K+-ATPase pump activity, or other mechanisms that affect changes in electrochemical potentials for ions could result in altered end-organ activity, in this case altered release, uptake, or storage of neurotransmitter.

Urinary catecholamine excretion was reported to be increased for salt-induced hypertension in Sprague-Dawley rats. In another group of animals, the addition of potassium chloride to the high salt diet reduced the magnitude of pressure increase and also resulted in attenuation of the increased urinary catecholamine excretion. Further, the decrease in blood pressure resulting from administration of the ganglionic blocking agent, chlorisodamine, to Sprague-Dawley rats on a high sodium and high potassium diet was diminished compared to the response obtained for animals on a high salt diet alone. However, baroreceptor control mechanisms and the response of blood pressure to sympathetic nerve stimulation were unaffected by the addition of potassium. The conclusion drawn from this study was that the addition of potassium to the high salt diet was capable of modifying the level of blood pressure by reducing the contribution of the central nervous system drive to the hypertension. Supporting this concept are observations obtained with a different experimental approach where the central pressor effects of intraventricular injections of angiotensin II or hypertonic saline were attenuated when hypertensive rats of the salt-sensitive Dahl strain were maintained on a high potassium diet.

Other observations suggest a possible mechanism for the interaction of K+ with neural transmission. Isolated strips of dog and rat arteries develop contractions when exposed to potassium-free solutions. This response can be reversed by increasing the potassium concentration of the bathing solution or by application of phenolamine. There is also evidence that re-uptake of norepinephrine by sympathetic nerve terminals...
diuretic, at least in the short term, and although effects on body fluid volumes are not as clear, it is possible that this is one mechanism by which it could alter blood pressure, especially in salt-dependent forms of hypertension.

Potassium and the Renin-Angiotensin System

Potassium chloride given both acutely\textsuperscript{38, 54, 55} and chronically\textsuperscript{51, 56} can suppress renin secretion rates. Based on observations in animals,\textsuperscript{56} it would appear that the ability of K\textsuperscript{+} to suppress renin secretion is critically dependent on the administration of K\textsuperscript{+} with the Cl\textsuperscript{−} anion, rather than K\textsuperscript{+} as KHCO\textsubscript{3}. Since potassium may also exhibit natriuretic effects, the direct suppression of renin activity by a high potassium intake could be overridden by a negative sodium or water balance. Thus, there may be a paradoxical increase in renin secretion following administration of diets of increased K\textsuperscript{+} content in some settings. This was demonstrated by Bauer et al.\textsuperscript{59} in 1979, who reported that in humans the plasma renin activity increased as the potassium intake increased, probably secondary to the relative Na\textsuperscript{+} or volume depletion. Administration of potassium chloride orally to dogs resulted in unchanged renin secretion unless adrenocorticotoid activity was fixed by means of exogenous administration following adrenalectomy.\textsuperscript{59} Under these conditions, KCl infusion decreased plasma renin activity and increased blood pressure.\textsuperscript{39} However, in intact dogs in which the infusion causes a significant natriuresis and negative sodium balance, the plasma renin activity was not affected.\textsuperscript{32}

The effect of potassium upon vascular reactivity through the renin-angiotensin system is not limited to alterations in renin activity. The dose response characteristics of angiotensin can also be altered by a high potassium diet.\textsuperscript{57, 58} The responses of arteriolar smooth muscle to angiotensin II or angiotensin III were diminished in animals on a high potassium diet, whereas angiotensin-stimulated aldosterone release by the adrenal was increased.\textsuperscript{57} Although the evidence is not in complete agreement, potassium probably results in a net increased adrenal steroidogenesis in response to angiotensin stimulation.\textsuperscript{57-59}

In humans, a low sodium, high potassium diet, which was associated with lowering the blood pressure of normotensives, was associated with an increase of both renin and aldosterone concentrations in plasma.\textsuperscript{21} In a different study, the effects of a high potassium diet were also evaluated in a group of normotensives where plasma renin activity and angiotensin II concentration were not changed, but aldosterone concentrations, renal blood flow, and adrenal and vascular responsiveness to angiotensin were all increased.\textsuperscript{40}

The effects of high potassium intake on experimental models of hypertension are equally difficult to assess. The addition of potassium to the drinking water of two-kidney, one clip Goldblatt hypertensive rats, which resulted in decreased blood pressure, also resulted in suppression of plasma renin activity, but increased aldosterone secretion.\textsuperscript{33} Although urinary excretion of electrolytes and volume were increased in both groups treated with K\textsuperscript{+}, body weights were comparable to control animals, suggesting no large changes in total body water or total body sodium. Nonetheless, specific compartment volumes and electrolyte contents were not reported. From these observations it would seem that blood pressure in this model might be most responsive to plasma renin activity directly, in spite of the aldosterone stimulation that occurred through mechanisms that were not reflected by increased serum potassium concentration.\textsuperscript{33} Recent experiments in our laboratory, where various potassium intakes were administered to two-kidney, one clip Goldblatt rats in varying ratios of Na\textsuperscript{+}/K\textsuperscript{+} in diets of constant total electrolyte intake, failed to result in any effect on the rate of development or level of hypertension. The rats exposed to the high potassium diet had elevated plasma renin activities and urinary aldosterone excretion compared to animals fed the control diet. These observations suggest subtle volume influences resulting from the concomitant low sodium content of the diet overrode any tendency for the high potassium intake to suppress plasma renin activity.\textsuperscript{34}

From these data, it is hazardous to speculate whether the antihypertensive effect of potassium could be related to its varied effects on the renin-angiotensin-aldosterone axis. In humans, when the dietary ratio of Na\textsuperscript{+}/K\textsuperscript{+} is decreased, plasma renin activity tends to be raised, which would not seem to support a vasodepressor or hypotensive effect mediated via variations in renin release directly. However, it is possible that the increased potassium results in reduced effective activity of circulating angiotensin on the vasculature under these conditions. Therefore, the increased plasma renin activity may not reflect accurately the biological vasopressor activity of angiotensin. The expected increased levels of aldosterone or other mineralcorticoids resulting from increased levels of angiotensin and enhanced adrenal responsiveness would, if anything, tend to result in sodium retention by the kidney and hence raise the blood pressure, rather than contribute to any antihypertensive effect.

Potassium as a Vasodilator

It has been recognized for several years that the potassium cation can act as a vasodilator by affecting arteriolar smooth muscle directly.\textsuperscript{45, 51, 52} Since potassium-induced vasodilation can be blocked by ouabain, this indicates that it is an active process dependent on a functional electrogenic sodium/potassium pump known to be present in vascular smooth muscle.\textsuperscript{61, 64} Although potassium is active as a vasodilator when given intraarterially, there is no evidence to suggest that increasing dietary potassium affects reductions of peripheral resistance chronically and in this way reduced arterial pressure. Nonetheless, the possibility of potassium having yet undocumented effects through an ouabain-sensitive-ATPase process is attractive, and this is an area of ongoing investigation.

Early observations by Overbeck and coworkers\textsuperscript{35, 36} indicated that vasodilation responses to infusions of
K+ were impaired in essential hypertensive men and in some models of Goldblatt, renal or genetic hypertension in animals. Based on these observations, Overbeck suggested that a circulating ouabain-like Na+-K+-ATPase inhibitor might be responsible for the impaired vasodilatory response. It was further suggested that these transport effects might be most directly reflected as hypopolarization of the cell membrane with resulting increased vascular tone.

Subsequently, evidence has evolved that the activity of the ouabain-sensitive-Na+-K+-ATPase is altered in many tissues of hypertensive humans and animals. Ouabain-sensitive-ATPase activity has been found to be decreased in rat tail artery and in cardiac muscle of volume-expanded experimental models of hypertension in dogs and rats and in leukocytes from patients with essential hypertension. These observations have led to the speculation that a natriuretic hormone, with ouabain-like characteristics that suppress the activity of the Na+-K+ pump, may play a role in hypertension. It is possible that increased potassium in the diet could antagonize the effect of a natriuretic hormone and thus reduce blood pressure in a manner similar to that by which potassium is known to antagonize the effects of digitalis toxicity, presumably by K+-stimulation of Na+-K+-ATPase.

Other observations suggest that sodium accumulation in cells of hypertensives could occur in the absence of primary inhibition of Na+-K+-ATPase. Although an abnormally high passive membrane permeability to sodium in erythrocytes from SHR (sodium-sodium exchange) has been reported, parallel findings were not observed in human RBCs of essential hypertensives. An abnormally low rate of extrusion of sodium by a furosemide-sensitive-Na+/K+ cotransport system in red blood cells (RBCs) of essential hypertensive patients may be associated with accelerated cellular Na+ extrusion via the active sodium-potassium pump. Yet other observations indicate that sodium/lithium countertransport (passive sodium/sodium exchange) is accelerated in RBCs of patients and their normotensive relatives with essential hypertension. The synthesis of these observations does not lead to any unifying hypothesis directly, although some of these alterations of ion transport phenomena could be interpreted as mechanisms that contribute to altered membrane potentials or electrochemical gradients, which in turn elicit increased tone of vascular smooth muscle.

Blaustein has presented the hypothesis that a sodium entry/calcium exit exchange mechanism in the sarcolemma contributes to the exquisite control of intracellular Ca++ activity which controls the level of arteriolar tone. The exchange movement of Ca++ and sodium is dependent on a favorable electrochemical gradient for movement of sodium from extracellular to intracellular compartments. Extrapolation of this hypothesis suggests that an ouabain-type inhibitor that results in subtle intracellular accumulation of sodium results in a less favorable gradient for sodium entry (and Ca++ exit) and increased vascular resistance. How K+ loading might influence this mechanism remains speculative. It would seem reasonable that increased potassium might in some way contribute to a more favorable gradient for sodium entry into the cell, perhaps through stimulation of a Na+-K+-ATPase that actively extrudes Na+ from the cell, which in turn results in a more favorable gradient for its passive entry in exchange for Ca++.

Conclusions

There is some evidence from both animal and human studies that varying the dietary intake of sodium and potassium may contribute to the control of blood pressure. Generally, in animal studies, an antihypertensive effect of a high potassium intake is most suggestive in salt-dependent forms of hypertension. The inconsistencies of the effect of potassium upon blood pressure in humans may be because it is only effective in those individuals genetically predisposed to more salt-dependent forms of hypertension.

If potassium has bona fide antihypertensive properties, the mechanism by which it exerts this activity remains unclear. The antihypertensive effect of potassium may be related to a diuretic activity, although this activity seems to be observed only when K+ is given in settings of increased total electrolyte intake. There is also evidence that it can influence the central and peripheral nervous system functions as well as the renin-angiotensin-aldosterone system. Since the therapeutic implications of real antihypertensive activity of potassium are great, the characteristics of these effects and the mechanisms by which they are mediated, hopefully, will be delineated in future studies of good experimental design.

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