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Postulating the major environmental condition resulting in the expression of essential hypertension and its associated cardiovascular diseases: Dietary imprudence in daily selection of foods in respect of their potassium and sodium content resulting in oxidative stress-induced dysfunction of the vascular endothelium, vascular smooth muscle, and perivascular tissues

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A B S T R A C T

We hypothesize that the major environmental determinant of the expression of essential hypertension in America and other Westernized countries is dietary imprudence in respect of the consumption of daily combinations of foods containing suboptimal amounts of potassium and blood pressure-lowering phytochemicals, and supraphysiological amounts of sodium. We offer as premise that Americans on average consume suboptimal amounts of potassium and blood pressure-lowering phytochemicals, and physiologically excessive amounts of sodium, and that such dietary imprudence leads to essential hypertension through oxidative stress-induced vascular endothelial and smooth muscle dysfunction. Such dysfunctions restrict nitric oxide bioavailability, impairing endothelial cell-mediated relaxation of the underlying vascular smooth muscle, initiating and maintaining inappropriately increased peripheral and renal vascular resistance. The biochemical steps from oxidative stress to vascular endothelial dysfunction and its pernicious cardiovascular consequences are well established and generally accepted.

The unique aspect of our hypothesis resides in the contention that Americans' habitual consumption of foods resulting in suboptimal dietary intake of potassium and supraphysiological intake of sodium result in oxidative stress, the degree of which, we suggest, will correlate with the degree of deviation of potassium and sodium intake from optimal. Because suboptimal intakes of potassium reflect suboptimal intakes of fruits and vegetables, associated contributors to oxidative stress include suboptimal intakes of magnesium, nitrate, polyphenols, carotenoids, and other phytochemical antioxidants for which fruits and vegetables contain abundant amounts. Currently Americans consume potassium-to-sodium in molar ratios of less than or close to 1.0 and the Institute of Medicine (IOM) recommends a molar ratio of 1.2. Ancestral diets to which we are physiologically adapted range from molar ratios of 5.0 to 10.0 or higher.

Accordingly, we suggest that the average American is usually afflicted with oxidative stress-induced vascular endothelial dysfunction, and therefore the standards for normal blood pressure and pre-hypertension often reflect a degree of clinically significant hypertension. In this article, we provide support for those contentions, and indicate the findings that the hypothesis predicts.

Introduction

Medical science has identified numerous syndromes characterized in part by hypertension linked pathogenically to a single gene mutation, so called monogenic hypertension [1]. No such thing as monogenic essential hypertension exists, a contradiction in terms. Nevertheless, genes do play an important role in the pathogenesis of essential hypertension. In the general population, researchers find hundreds if not thousands of genes that have variant alleles that have a small effect on blood pressure, 1 mm Hg or less [1]. In a given person, when the number of such risk alleles increases, so does the probability that hypertension will occur, depending on environmental factors [1]. In this article we postulate that certain patterns of dietary intake constitute the most important environmental condition permitting the expression and determining the severity of hypertension in genetically susceptible persons.

Medical scientists, including physiologists and practitioners, have struggled for more than a century with the clinical problem of essential hypertension, its pathogenesis and treatment [2,3]. Less attention has been devoted to prevention. By way of a simple hypothesis we offer in this article a potential contribution for both prevention and treatment of essential hypertension.

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The hypothesis. [We] still lack a thorough understanding of the primary etiologies that lead to chronically elevated blood pressure [4].

We hypothesize that Americans, and most people in Westernized countries, habitually consume a self-selected daily diet of foods that contain exceedingly suboptimal amounts of dietary potassium and enormously supraphysiological amounts of sodium chloride [5], a dietary imprudence that causes oxidative stress, which in turn causes dysfunction of the vascular endothelium, vascular smooth muscle, and perivascular tissues. Such dysfunction ultimately results in hypertension, its associated cardiovascular diseases, and salt sensitivity of blood pressure.

Although this article will focus on dietary intake of potassium and sodium as causes of oxidative stress, we recognize that "a daily diet of foods that contain suboptimal amounts of dietary potassium" also contains suboptimal amounts of other molecular species with blood pressure regulating properties. Potassium-rich foods, predominantly fruits and vegetables, for example, also contain abundant magnesium [6], a variety of antioxidants (e.g., polyphenols, vitamins C and E) [7,8], carotenoids [9], and vasodilator precursors (e.g., nitrate) [10], any or all of which may be as important to consider.

Because fruits and vegetables are the richest dietary source of potassium, our hypothesis speaks to a greatly suboptimal intake of fruits and vegetables in regard to the most important environmental condition permitting expression and determining the severity of essential hypertension in genetically susceptible persons. Likewise, because processed foods and restaurant foods supply the major fraction (> 75%) of sodium in the average American diet [11], our hypothesis also speaks to greatly excessive intake of processed and restaurant foods in regard to the root cause of essential hypertension.

Evaluation of the hypothesis

Establishing that the foods that Americans habitually consume contain suboptimal (subphysiological [5]) amounts of potassium on average

Four lines of evidence support the argument that Americans on average suffer from a moderately severe habitual degree of potassium depletion due to a greatly suboptimal dietary potassium intake:

- The failure of Americans on average to meet the Institute of Medicine's (IOM) recommended amount of food consumption of potassium;
- The failure of the IOM's expert panel on nutrition to adopt an evolutionary perspective in determining the amount of dietary potassium consumption for which humans are genetically and physiologically adapted;
- The numerous health benefits of enriching the diet in potassium, with food or supplements.
- The deleterious effects of reducing dietary potassium intake below the current amount consumed on average.

For the 21st century, the expert panel on nutrition of the Institute of Medicine (IOM) has specified an "Adequate Intake (AI)" for potassium, namely that adults consume at least 120 mmol (mmol) [4700 mg] of potassium per day, except for those with diseases that render them potassium intolerant [12]. Americans have largely ignored that guideline or do not know about it. Table 1 shows the average values for potassium consumption by Americans (2005–2010) [13]. The values for 2013–2014 are similar, 60–80 mmol per day.

Note in Table 1 that average consumption of potassium in amounts of 60–80 mmol per day by adults falls well below the IOM recommended amount of 120 mmol per day, with American women consuming half the recommended amount on average, and American men about two-thirds. The findings do not indicate improvement in achieving "adequate intakes" in 2010–2013 over the findings reported for years 2003–2004.

Given that the IOM based their recommendation on informed analysis of the presumably best estimate of the intake rate of potassium for optimal health—but not a necessarily sufficient one for that purpose—we must conclude that Americans on average remain in a persistent state of potassium deficiency. Elderly persons may be more potassium deficient than younger persons as total body potassium declines with age [14].

The World Health Organization (WHO) recommends potassium consumption from food at the level of 90 mmol/day (3519 mg/day) and a molar ratio of potassium-to-sodium of 1.0, with the proviso that if sodium intake increases to a level that renders the ratio less than 1.0, potassium intake be increased to maintain a ratio of 1.0 [15]. Thus if sodium intake were 150 mmol/day (3450 mg/day), potassium intake should be increased to 150 mmol/day. We will argue from an evolutionary perspective, in another section below, for a much higher potassium-to-sodium molar ratio than 1.0, specifically 5.0 to 10.0 or higher, as optimal (see Table 1).

While 120 mmol of potassium consumption per day would certainly improve body potassium content by comparison with what Americans currently consume on average, no evidence indicates that 120 mmol of potassium per day provides the amount necessary for optimal physiological health. Estimates of adequate potassium intakes from an evolutionary perspective would suggest that 120 mmol per day still falls far short of optimal [16]. The lineage of our species, *Homo sapiens,* subsisted as hunters-gatherers for at least 5 million years, during which time they adapted to dietary intakes of potassium in the range of 200–400 mmol per day on average [16-18]. Because *Homo sapiens* evolved only in the last 1–2% of that 5 million year lineage, we can conclude that too little time has elapsed for the requirement for adapted potassium consumption to have changed, given that conserved core metabolic processes depend on potassium (see review by Palmer [18]). Palmer also states that "*The normal kidney has the capacity to maintain K^+ homeostasis in the setting of high dietary intake. As an example, serum K^+ levels are maintained in the normal range even when dietary K^+ intake is increased to approximately 15 g/d (586 mmol/d) for 20 days* [18].

A third line of evidence that Americans consume suboptimal amounts of potassium emerges from studies that indicate numerous health benefits when potassium intake increases, either from food sources or from supplements of potassium [18-32]. Also indicative, "*Inadequate consumption of K + combined with excessive intake of Na + contributes to the pathophysiology of various chronic diseases such as obesity, hypertension, diabetes, kidney stones, and bone disease* [18]." Aburto and colleagues conclude from their study of the literature:

> "High quality evidence shows that increased potassium intake reduces blood pressure in people with hypertension and has no adverse effect on blood lipid concentrations, catecholamine concentrations, or renal function in adults. Higher potassium intake was associated with a 24% lower risk of stroke (moderate quality evidence). These results suggest that increased potassium intake is potentially beneficial to most people without impaired renal handling of potassium for the prevention and control of elevated blood pressure and stroke [33]."

Intervention studies in which investigators have increased potassium intake demonstrate significant reductions in blood pressure and in the incidence of those cardiovascular diseases for which hypertension predicts an increased risk [18,23,25,30,33–42].

Conversely, patients with low dietary intakes of potassium have a greater risk of hypertension [43], and increased sensitivity to blood pressure increases with sodium loads [44].

Plasma potassium concentration is sensitive to reduction in potassium intake and more so as potassium intake approaches the minimum average intake for Americans [28]. The effects are exaggerated with higher sodium intakes [28].

The exaggerated anti-hypertensinogenic effect of potassium at high

Table 1
Potassium and sodium consumption of various diets, and their potassium-to-sodium ratio.

Category	Na, mg/day	K, mg/day	Na, mmol/day	K, mmol/day	Na/K mg/mg	Na/K, mmol/mmol	K/Na mg/mg	K/Na, mmol/mmol
Current American Diet	3505	2668	152	68	1.31	2.23	0.76	0.45
IOM Recommended Diet	2300	4700	100	120	0.49	0.83	2.04	1.20
Ancestral Diet #1	1150	11,730	50	300	0.10	0.17	10.20	6.00
Ancestral Diet #2	920	11,730	40	300	0.08	0.13	12.75	7.50
Ancestral Diet #3	690	11,730	30	300	0.06	0.10	17.00	10.00
Ancestral Diet #4	1150	9775	50	250	0.12	0.20	8.50	5.00
Ancestral Diet #5	920	9775	40	250	0.09	0.16	10.63	6.25
Ancestral Diet #6	690	9775	30	250	0.07	0.12	14.17	8.33

dietary sodium intakes reflects in part the effect of potassium to suppress sodium-induced endothelial production of transforming growth factor beta (TGF-ß), a growth factor that causes morphological changes that promote hypertension (arterial stiffness, hypertrophy of vascular smooth muscle, increased local production of extracellular matrix proteins [45,46]).

Excerpts from the literature support and amplify the above contentions:

> "Most published studies confirmed a BP-reducing effect by potassium intake either by consumption of more fruits and vegetables, salt-substitutes and enrichment, or supplementation; and these studies suggest that it also plays a cardioprotective role. ...In addition to BP reduction, dietary potassium supplementation improved measures of endothelial function, vascular compliance, and cardiovascular structure and functional parameters [34]."
> "Potassium and sodium share a yin/yang relationship in the regulation of blood pressure (BP). BP is directly associated with the total body sodium and negatively correlated with the total body potassium...Hypertensive cardiovascular damage, stroke and stroke-related death are accelerated by salt intake but could be prevented by increased dietary potassium intake [39]."
> "In the absence of chronic kidney disease, the combined evidence supports a diet high in potassium content serves a vasculoprotective function, especially in the setting of salt-sensitive hypertension and prehypertension [39]."

Establishing that potassium deficiency increases intracellular acidity

As we will discuss subsequently, increased intracellular acidity can contribute to dysfunction of the vascular endothelial cell and the underlying vascular smooth muscle. Physiologists have known for decades that cellular deficiency of potassium increases cellular acidity, in particular when caused by reduction in dietary potassium [47-53]. See Fig. 1 in [50].

Salt loading also increases intracellular acidity [54]. The suboptimal fruit and vegetable content of the American diet is net acid producing, which also contributes to abnormally increased intracellular acidity. Krupp et. al. report: "*Our results show, for the first time in a comparative analysis of a large representative population sample, significant relationships of BP and hypertension prevalence with questionnaire- and biomarker-based estimates of potassium intake and with an estimate of dietary acid load.*"[55]

Therefore, in the circumstance in which a person consumes suboptimal amounts of dietary potassium and supraphysiological amounts of dietary sodium, we would find intracellular acidity at greater than optimal for physiological health.

Establishing that Americans consume supraphysiological amounts of sodium on average

Three lines of evidence indicate that Americans consume supraphysiological amounts of sodium:

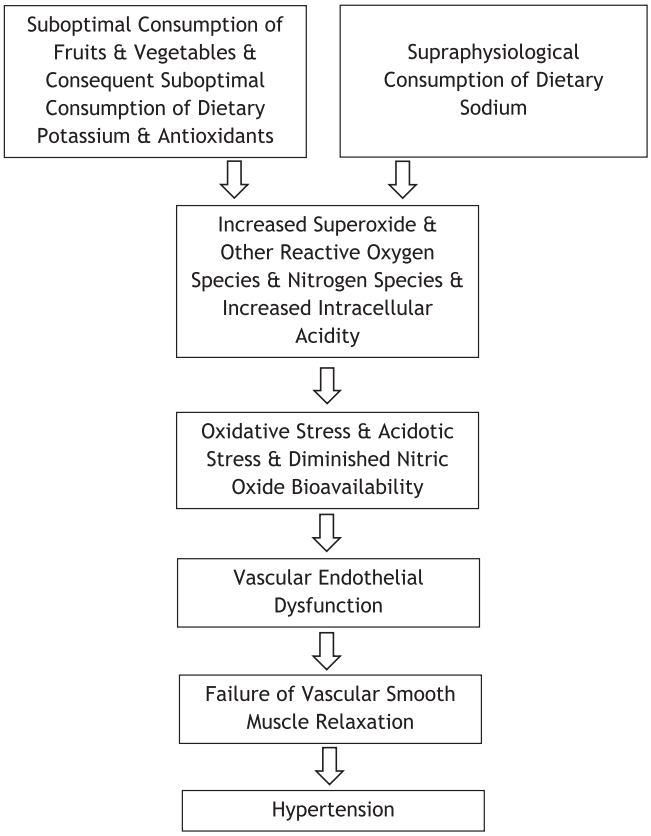

Fig. 1. Basic depiction of the hypothesis.

- Failure of Americans to consume sodium at or below the amount that the IOM considers the upper tolerable limit;
- Failure of the IOM to adopt an evolutionary perspective in assigning a tolerable upper limit of sodium consumption per day;
- Studies of the health benefits of limiting sodium intake well below the IOM's tolerable upper limit.

The IOM recommends that adults consume no more than 100 mmol of sodium per day [56]. Yet Americans consume between 120 and 190 mmol of sodium per day or more [57]. Therefore, Americans consume more sodium than the IOM considers the upper tolerable limit for healthy eating.

Most Americans do not know the recommended sodium intake [58].

From an evolutionary perspective, the IOM has set the tolerable upper limit for sodium consumption at too high a value. Estimates of ancestral human consumption of sodium per day amount to less than 50 mmol per day [17,59,60]. Because our ancestral lineage extends back 5–7 million years we argue that such low sodium intakes represent intakes to which we are genetically adapted.

Aburto and colleagues performed a meta-analysis of 37 randomized controlled trials of studies on the effect of reducing sodium intake of

blood pressure [61]. They found that reduction in sodium intake significantly reduced resting systolic and diastolic blood pressure. At sodium intake less than 2000 mg/day (87 mmol/day) versus greater intakes, systolic blood pressure decrease by 3.47 mm Hg and diastolic blood pressure by 1.81 mm Hg.

We would argue that those studies represent much smaller reductions in blood pressure than would have occurred had sodium intake been reduced to less than 30–50 mmol/day along with an increase in potassium intake to 250–300 mmol/day.

One might raise the concern that 30–50 mmol/day of sodium consumption might lead to total body sodium depletion. Strauss and colleagues have found that maintaining persons on a sodium intake of just a few mmol/day, enough to compensate for extrarenal losses of sodium, did not represent a state of physiological sodium depletion inasmuch as *"In this condition, the addition of a minute increment to the body content of sodium leads to an immediate increase in renal sodium excretion* [62]."

Hypertension is a major risk factor for cardiovascular and cerebrovascular disease, and significant reductions in risk is associated with programs that reduce sodium intake [63]. A pooled analysis of studies in both hypertensive and normotensive persons found that a reduction in sodium intake of about 75 mmol per day for four weeks or longer resulted in a significant and important reduction in blood pressure [64]. Even though the reduced value of sodium intake remained in the supraphysiological range, the study showed that blood pressure reduction occurs in proportion to the reduction in sodium intake [64].

The investigators, He and MacGregor, recommend reduction in sodium intake to approximately 50 mmol per day [64], an amount closer to optimal depending on concomitant potassium intake (see Table 1).

In subjects with Stage I hypertension, the higher the baseline blood pressure the greater the reduction in blood pressure when sodium intake is reduced from 150 to 50 mmol/day [65].

A few quotes from the literatures support and amplify those concepts:

> "The most recent data, from 2013-14, indicates average daily U.S. sodium intake is [148 mmol] 3,409 mg, excluding salt added at the table, with 44% of intake from 10 and 70% from 25 food types; 61% from foods obtained at the store; and sodium density highest from foods obtained at restaurants [66]. Food types contributing to intake differ by race/ethnic group… Sodium intake remains high and comes from a variety of food types and places [67]."
>
> "In summary, in SS [salt-sensitive] blacks, we find that dietary NaCl loading induced renal vasoconstriction whose extent varied directly with that of the attending pressor effect of NaCl. Supplemental KHCO3 abolished the pressor effect of NaCl [68]."

Summary of vascular endothelial function related to regulation of blood pressure and the consequences of dysfunction of such vascular endothelial activity

The regulation of arteriolar smooth muscle tone involves numerous pathways. The best studied and most important consists of the pathway involving the vascular endothelial production of nitric oxide (NO), a soluble gas that diffuses to the underlying vascular smooth muscle, and induces relaxation of the smooth muscle.

With each stroke volume during systole the shear stress of the blood flow on the gel-like membrane (the glycocalyx) separating the endothelial membrane and the lumen of the vessels causes the endothelial cell to release a puff of nitric oxide, which in turn activates the nitric oxide receptor, soluble guanylyl cyclase, generating cyclic GMP [69]. Cyclic GMP increases intracellular calcium, which leads to hyperpolarization of the endothelial membrane potential.

The way an increase the intracellular calcium leads to endothelial membrane hyperpolarization involves activation of calcium-activated potassium ion channels, which release potassium ions from the endothelial cell.

The endothelial hyperpolarization conducts through cell-to-cell junctions to hyperpolarize the vascular smooth muscle, thereby causing relaxation of the muscle, reducing the resistance of the arterial blood flow, thus lowering blood pressure.

In addition to the conduction of the hyperpolarization to underlying smooth muscle via gap junctions, hyperpolarization of the smooth muscle is contributed to by the potassium ions accumulating in the interstitial space that bathes the muscle cell. The hyperpolarization occurs in large part because potassium stimulates membrane-bound Na + K + ATPase.

The membrane resistance of the vascular smooth muscle permits even small changes in electrochemical gradient to have important effect on membrane potential and therefore on the decrease in vascular muscle tone and an increase in arteriolar diameter [70].

Gutterman states:

> "[In] VSMCs [vascular smooth muscle cells]…even small changes in the electrochemical gradient can significantly alter membrane potential and vascular diameter. Vascular resistance resides mostly in the microcirculation where small changes in arteriolar diameter can result in large changes in conductance and flow as predicted by Poiseuille's law. A 20% reduction in arteriolar diameter yields > 100% increase in resistance and reduces flow by > 50% [71]."

Describing oxidative stress and summarizing how it impairs vascular endothelial function related to regulation of blood pressure

Halliwell and Gutteridge define oxidative stress as: *"oxidative stress is a disturbance in the pro-oxidant– antioxidant balance in favour of the former, leading to potential biomolecular damage caused by attack of reactive species upon the constituents of living organisms."* [71]

Oxidative stress occurs as a disorder of normal oxidation-reduction (redox) signaling reactions involving reactive oxygen species (ROS), including oxygen free radicals.

Halliwell and Gutteridge [71] define free radicals as:

> "free radical is any species capable of independent existence (hence the term 'free') that contains one or more unpaired electrons. An unpaired electron is one that occupies an atomic or molecular orbital by itself. A hydrogen atom has only one electron, which must therefore be unpaired".

Most free radicals act as oxidizing agents (oxidants). They define reactive oxygen species as:

> "Reactive oxygen species (ROS) is a collective term for species derived from O2 that are more reactive than O2 itself. The term includes not only superoxide ($O^{-\cdot}$) and some other oxygen radicals, but also some non-radical derivatives of O2, such as H2O2 and hypochlorous acid (HOCl). Hence all oxygen radicals are ROS, but not all ROS are oxygen radicals. 'Reactive' is a relative term; and H2O2 are selective in their reactions with biological molecules, leaving most of them unscathed, whereas $OH^{\cdot}$ attacks everything around it".

In the cell, most ROS act as oxidizing agents (oxidants), removing electrons from other molecules, including macromolecules, in the process becoming reduced. Some oxides of nitrogen, such as nitric oxide ($NO^{\cdot}$), are free radicals generated by cells and are referred to as reactive nitrogen species (RNS). To maintain balance (redox balance) cells also produce antioxidants including enzymes that catalyze the metabolism of ROS, and molecules that scavenge free radicals.

ROS/RNS can have important physiological roles. For example, nitric oxide has numerous important physiological functions including regulation of vascular smooth muscle tone, platelet aggregation and adhesion, and certain central nervous system physiological functions [72].

Oxidative stress occurs when the rate and the amount of ROS/RNS

exceeds the rate of which the antioxidant mechanisms can maintain redox balance. Oxidative stress-induced vascular endothelial dysfunction is associated with inflammation [73,74]. Esper states: *Cardiovascular risk factors cause oxidative stress that alters the endothelial cells capacity and leads to the so called endothelial "dysfunction" reducing its capacity to maintain homeostasis and leads to the development of pathological inflammatory processes and vascular disease* [74].

The major molecular mechanisms by which oxidative stress induces vascular endothelial and smooth muscle dysfunction have been well established [75–82]. NADPH oxidase is a major generator of superoxide, and superoxide generates a cascade of reactions that generate multiple reactive oxygen species. NADPH oxidase activation occurs from the variety of mechanisms, including the shear stress caused by the pressure of blood flowing against the endothelium during systole. Vasoactive agonists such as angiotensin II can also activate NADPH oxidase [83]. Salt loading also increases NADPH oxidase [84].

Superoxide generated by NADPH oxidase reacts with nitric oxide to produce peroxynitrite, which promotes uncoupling of nitric oxide synthase, thereby reducing nitric oxide availability. The enzyme superoxide dismutase catalyzes the conversion of superoxide to hydrogen peroxide, which can deleteriously cause inflammation and fibrosis of vascular smooth muscle.

A few quotes from the literature support and amplify those concepts:

> "A major mechanism for the impact of oxidative stress on vascular tone is the decrease of nitric oxide (NO) bioavailability and/or signaling, leading to endothelial dysfunction, and ROS may also promote vascular cell proliferation and migration, inflammation and apoptosis, as well as extracellular matrix alterations [85]."
> "When this redox balance is perturbed, because of either increased ROS production or decreased antioxidant capacity, oxidant stress is increased in the vessel wall and, if not offset, vascular dysfunction ensues [86]."
> "[I]n vascular disease states, such as hypertension and hypercholesterolaemia, excessive production of ROS may overwhelm the antioxidant defence mechanisms of cells, resulting in 'oxidative stress', damage to the artery wall and, ultimately, development of atherosclerotic plaques [87]."
> "Increased generation of ROS has been demonstrated in experimental and human hypertension [88]."
> "Oxidative stress in blood vessels and the kidney in hypertension can be induced by diverse vasoconstrictor mechanisms, including blockade of nitric oxide synthase and activation of angiotensin II type I receptors and thromboxane receptors. It can cause vasoconstriction via bioinactivation of nitric oxide, and by nitric oxide synthase-independent mechanisms that include increased generation of endothelin-1 and the effects of superoxide anion and hydrogen peroxide on vascular smooth muscle cells [89]."
> "Therefore, our results suggest that, in the Dahl salt-sensitive rat, increased oxidative stress is associated with salt-dependent hypertensive nephrosclerosis and that decreased NO· bioavailability may represent a common factor responsible for the vascular and glomerular dysfunction [90]."

Establishing the role and mechanism whereby oxidative stress arises as the consequence of sub-optimal dietary potassium, supraphysiological dietary sodium, and increased intracellular acidity

Given that potassium reduces blood pressure and that sodium increases it, and given that hypertension results from oxidative stress-induced dysfunction of the vascular endothelium, we should not dismiss the possibility that suboptimal dietary intake of potassium and supraphysiological dietary intake of sodium play a central role in the pathogenesis of essential hypertension. Since optimal dietary intake of potassium would necessitate greatly increase intake of fruit and vegetables, we should likewise not dismiss the role of the accompanying greatly increased intake and variety of blood pressure regulating phytochemicals.

Potassium and oxidative stress

Potassium deprivation increases activity of NADPH oxidase [91] and high potassium decreases the activity of NADPH oxidase [92,84,93,94]. Potassium also indirectly decreases the activity of NADPH oxidase by stimulating the production of nitric oxide [95], which decreases the activity of NADPH oxidase [96]. High potassium also stimulates Na + K + ATPase, which hyperpolarizes the plasma membrane and stimulates nitric oxide formation [97].

One of the contributors to the development of oxidative stress with dietary imprudence of potassium and sodium is an increase in the production of asymetric dimethylarginine (ADMA), an inhibitor of nitric oxide synthase and as a consequence a reduction in nitric oxide bioavailability [98]. A high dietary potassium intake decreases ADMA levels, increasing nitric oxide bioavailability, and reducing blood pressure in salt sensitive subjects [99].

Potassium depletion induced by reducing dietary potassium increases superoxide production and sensitizes arteries to vasoconstriction [100].

Small increases plasma potassium concentration as occurs with increased dietary potassium intake decrease free radical formation in vascular endothelial cells and reduces renovascular resistance [28].

Given that fruits and vegetables provide the richest source of dietary potassium as well as a rich source of phytochemical antioxidants and other blood pressure lowering substances, we are not surprised by the findings of McCall and colleagues that increases in the number of servings of fruit and vegetables improves an established marker of vascular endothelial function and increases vascular relaxation in hypertensive patients in a dose dependant manner [32].

The findings of many researches support and amplify those concepts [28,95,99–106].

Sodium and oxidative stress

A high sodium diet results in oxidative stress-induced vascular endothelial dysfunction and consequent reduced nitric oxide bioavailability and impaired vasodilatation. High sodium diets increase oxidative stress and reduce nitric oxide bioavailability by decreasing the activity of nitric oxide synthase [107]. High sodium intakes increase the production of reactive oxygen species which play an important role in inducing vascular endothelial dysfunction and reducing endothelial mediated vasodilation (see references in [108]). Salt loading increases NADPH oxidase activity and superoxide production and expression [93]. Dietary sodium restriction improves vascular endothelial function by increasing nitric oxide bioavailability [109]. Dietary sodium restriction improves nitric oxide production by enhancing the production of the nitric oxide synthase cofactor, tetrahydrobiopterin (BH4) [110].

In normotensive persons, a high sodium meal significantly increases plasma sodium concentration and blood pressure transiently, and increases blood pressure as a linear function of the increase in plasma sodium concentration [21]. Suckling et al. state: "*A potential mechanism whereby dietary salt could increase BP is through its effects on plasma sodium concentration*". Earlier studies had shown that plasma sodium concentration stiffens vascular endothelium and reduces nitric oxide release [111]. The reduction in endothelial nitric oxide synthase activity associated with high sodium diets is mediated by the small increase in plasma sodium concentration that occurs with the high salt intake [112].

In essential hypertension NADPH oxidase activity is increased [113], resulting in the production of superoxide anion and a subsequent cascade of reactive oxygen species.

High sodium diets increase NADPH oxidase activity in the

hypothalamus, leading to centrally mediated sympathetic activity and increased blood pressure [114].

Most physiologists who study the role of sodium intake in the pathogenesis of hypertension distinguish between two groups, salt sensitive subjects and salt resistant subjects. The distinction is based on the blood pressure response to a large salt load, with salt sensitive subjects failing to vasodilate significantly and salt resistant subjects vasodilating significantly [115]. We argue that there might not be two separate groups, rather only one group with differing degrees of salt sensitivity. Even though some subjects vasodilate to an appreciable degree, we do not know that their degree of vasodilation is optimal.

Considering as one group all the subjects studied with large acute salt loads, including those who have met the criteria for salt sensitivity and those who have met the criteria for salt resistance: if we constructed a frequency distribution chart for delta systemic vascular resistance and found a bell shaped distribution with only one peak, how could we justify the claim that there really are two groups, one salt sensitive and one salt resistant. It seems that we could justify the claim that there is one group only, namely a salt sensitive group with differing degrees of salt sensitivity. Indeed, DuPont et al. [116] have found that persons who meet the criteria for salt resistance nevertheless exhibit impaired endothelial dependent vasodilation during consumption of a very high salt diet.

We could further argue that it is unlikely that anyone could be salt resistant, even though they showed some degree of vasodilation, inasmuch as no one really consumes habitually a diet of foods containing optimal amounts of potassium and only physiological amounts of sodium, amounts we submit are 250–300 mmol/day and less than 50 mmol/day, respectively. Any amounts lesser for potassium and greater for sodium would be associated with some degree of oxidative stress-induced vascular endothelial dysfunction and correspondingly some degree of reduced nitric oxide bioavailability.

We could further argue that a diet of foods containing suboptimal amounts of potassium and supraphysiological amounts of sodium would also contain suboptimal amounts of magnesium, nitrate and polyphenols, which would contribute to reduced nitric oxide bioavailability.

An optimal selection of foods should have a molar potassium-to-sodium ratio between 5.0 and 10.0 or higher. To accomplish that would entail consuming lots of fruits and vegetables, which also would make the diet rich in nitrate and polyphenols.

Incidentally such a diet would be net base producing and causal of a subclinical metabolic alkalosis [16,117]. No one has to our knowledge studied the effect of low grade subclinical metabolic alkalosis caused by a net base producing diet on the efficacy of nitrate conversion to nitric oxide or the efficacy of the antioxidant effect of polyphenols. Likewise, because each antioxidant enzyme has a pH optimum, we do not know whether the pH shift from a net acid to a net base producing diet could increase or decrease their enzymatic activity.

The glycocalyx and sodium

The luminal surface of the vascular endothelium does not contact the blood compartment directly because it has an intervening gel-like layer consisting of proteoglycans linked to the endothelial membrane and covalently to glycoaminoglycans, glycoproteins, and glycolipids. The glycoaminoglycans consist predominantly of heparan-sulphates and hyaluronate, poly-anions that can bind sodium ions. The poly-anions of the glycocalyx bind sodium ions without commensurate water, and buffer a substantial fraction of the increased delivery of sodium that accompanies consumption of a high sodium meal, thus restricting the increase in extracellular volume that would otherwise occur, releasing it between meals [118]. An intact glycocalyx therefore mitigates the hypertensinogenic effect of consuming high sodium meals. However, if sodium intake occurs at very high levels or too often, the poly-anions can be shed and allow sodium ions to reach the endothelial membrane directly and enter the cell through sodium channels [119,120], thereby stimulating production of the nitric oxide synthase inhibitor, asymmetric dimethylarginine (ADMA) and activate the superoxide generating NADPH oxidase, both of which reduce nitric oxide bioavailability. (See Fig. 1 in [82])

Components of the glycocalyx can transduce the mechanical shear stress produced by the intraluminal blood flow and thereby increase production of nitric oxide. High plasma sodium concentrations cause a stiffening of the subendothelial cytosol and prevent normal production of nitric oxide [119,120].

High salt diets can also induce inflammatory changes in the vascular endothelial wall and contribute to vascular endothelial dysfunction. The mechanisms whereby that occurs has been well described [121-127].

Acidity and oxidative stress

Intracellular acidosis can release iron bound to protein, which then can lead to production of very destructive hydroxyl radicals [128]. Because the activity of enzymes peaks at their optimal pH, increased intracellular acidity might reduce the activity of antioxidant enzymes, in particular because they evolved in the more alkaline environment of a high potassium-to-sodium ratio (see below).

Importance of the potassium-to-sodium ratio

Many investigators have stressed the importance of the sodium potassium ratio [129–137].

> "Our data indicate that when people have an increased intake of potassium, high intake of sodium is not associated with higher BP [138]."
>
> "The highest blood pressures were observed in the group with the highest estimated sodium excretion and the lowest estimated potassium excretion (difference from group with lowest sodium excretion and highest potassium excretion, 12 mm Hg in systolic pressure and 5 mm Hg in diastolic pressure [139]."

Importance of the bicarbonate-to-chloride ratio

Because the current American diet contains suboptimal amounts of potassium it also contains suboptimal amounts of bicarbonate precursors, organic anions combustible to bicarbonate, that charge-balance the potassium cation. As discussed earlier, that contributes to the sub-physiological intracellular pH (increased acidity) which might affect the activity of antioxidant enzymes, reducing their effectiveness.

The supraphysiological amounts of the cation sodium in the American diet has chloride as sodium's charge-balancing anion, making high sodium diets also high chloride diets, thus high sodium chloride, or salt, diets. Compared to the hunter-gatherer diet of our pre-agricultural ancestors to which we are genetically physiologically adapted, the American diet has a subnormal ratio of bicarbonate-to-chloride. We know little about the potential adverse effects specifically of the supraphysiological amounts of chloride in the diet. See review by McCallum et al. and references therein [140].

Kurtz and Morris found that uninephrectomized rats given deoxycorticosterone and sodium chloride increased blood pressure significantly greater than those given sodium as the bicarbonate salt or the acetate salt [141]. In humans, bicarbonate-rich mineral water lowered blood pressure under conditions in which the same amount of sodium chloride did not [142,143].

More recently, Tanaka et al. investigated the effects of potassium chloride and potassium bicarbonate on blood pressure, frequency of stroke and severity of the renal lesions in the stroke prone spontaneously hypertensive rats, finding that potassium chloride induced significantly greater increases in blood pressure than did potassium

bicarbonate [144].

Thus it appears that the chloride anion contributes to the hypertensinogenic effect of high sodium chloride diets.

Implications of the hypothesis

Because the average American consumes foods containing suboptimal amounts of potassium and physiologically excessive amounts of sodium under their usual conditions of daily living, such individuals will already have some degree of oxidative stress. That would imply also that such individuals have some degree of vascular endothelial dysfunction and blood pressures that are already higher than optimal. Accordingly, determining optimal levels of blood pressure will necessitate dietary intervention studies with Americans consuming optimal amounts of potassium and sodium (say, 250–300 mmol/day potassium and less than 50 mmol/day sodium). Such studies will establish new standards for what constitutes hypertension and pre-hypertension.

Given that oxidative stress-induced vascular endothelial dysfunction already exists with potassium intakes of ~60 mmol per day, and that blood pressures in so-called normotensive individuals might already be abnormally high to a moderate degree, long-term high salt loads might not increase blood pressures further [145]. The failure of blood pressure to increase with increasing salt loads in such subjects might be attributable to the persistence of significant antioxidant mechanisms before morphological changes in the vascular wall eventually develop.

We do not intend our hypothesis to exclude other components of potassium-rich, sodium-poor foods as contributing factors in eliminating oxidative stress in the vasculature; antioxidant vitamins C and E, and polyphenols in fruits and vegetables may contribute to some degree, and possibly be most effective in a potassium-rich, sodium-poor environment [146]. Likewise, foods rich in potassium are likely to be rich in nitrate, which should be expected to increase nitric oxide bioavailability.

Testing the validity of the hypothesis

The hypothesis predicts that apparently healthy so-called normotensive persons already have some degree of oxidative stress under the circumstances of daily living due to their habitual consumption of foods containing suboptimal amounts of potassium and associated antioxidants, and foods containing excessive amounts of sodium. To test the validity of that prediction we recommend making measurements in blood and urine of markers of oxidative stress in such persons on a fixed diet similar to that of their typical daily diet and repeating those measurements on the same persons on a fixed diet containing 250–300 mmols per day of potassium and 50 mmols per day of sodium chloride. Finding that the oxidative stress markers significantly decline in the steady-state on the higher potassium, lower sodium diet would support the hypothesis. Finding no significant change would falsify the hypothesis, if the sample size was sufficient to give the test adequate power.

Testing whether the recommended high potassium/antioxidant low sodium diet prevents the occurrence of hypertension in genetically susceptible persons would require longitudinal intervention studies of very long duration. Presumptive evidence of the diet's prevention potential could be obtained by examining the effect of the diet in persons with existing hypertension. The finding that the recommended high potassium/antioxidant low sodium diet normalized blood pressure and maintained it so in the steady-state would strongly support the prevention potential of the diet.

The above studies would best be performed as inpatient studies on a metabolic ward where dietary amounts can be controlled and non-dietary conditions promoting oxidative stress (e.g., air pollution, sedentism, sleep deprivation) can be minimized or eliminated.

Does currently available data warrant government and academic societies to reconsider current recommendations for dietary sodium and potassium?

We suggest that currently available data extensively described in this article warrant reconsideration of current recommendations for consumption of foods with the specified higher levels of potassium/antioxidants and lower levels of sodium by the Institute of Medicine, United States Department of Agriculture, and academic societies that advise clinicians and the public on prevention and treatment of hypertension.

Practical concerns in achieving the dietary goals suggested by the hypothesis

Humanity's worldview and self-conception, and the ecological, social, economic, political, and medical crises that stem from them, render it impractical for a global change to a diet of much higher intake of fruits and vegetables plus much lower intake of sodium chloride. Many populations struggle to obtain even enough food to survive. For Americans, a diet of packaged and processed foods, which typically provide physiologically excessive amounts of sodium and suboptimal amounts of potassium/antioxidants, cost far less than a diet that emphasizes large amounts of fresh fruits and vegetables. Perhaps the best hope lies in the potential for close-knit communities to adopt the recommended diet.

Predictions of the hypothesis

Dietary intervention studies in individuals over a range of molar potassium-to-sodium ratios will consistently show a highly significant inverse relationship with blood pressure. Such studies could be carried out in individuals with differing fixed steady-state sodium consumption amounts over a range of potassium consumption amounts spanning the range from contemporary to ancestral amounts, and vice-versa for sodium with differing steady-state potassium consumption amounts.

Given that oxidative stress-induced dysfunction of the vasculature imposes an increased risk of related cardiovascular diseases (e.g., atherosclerosis, coronary heart disease, stroke), habitual consumption of foods containing optimal amounts of potassium and sodium will greatly reduce the incidence of those diseases.

Conclusion

Nature is the cure of illness. Leave thy drugs in the chemist's pot if thou can heal the patient with food. —Hippocrates, 460–370 BCE

We have put forward an hypothesis postulating that essential hypertension in America and other Westernized countries results from dietary imprudence in respect of the selection of daily assortments of foods containing in total suboptimal amounts of potassium and supraphysiological amounts of sodium intake, in genetically susceptible persons. We offer as premise that Americans on average consume suboptimal amounts of potassium and physiologically excessive amounts of sodium, and that such dietary imprudence leads to essential hypertension through oxidative stress-induced vascular endothelial and smooth muscle dysfunction. Such dysfunctions restrict nitric oxide bioavailability, impairing endothelial cell-mediated relaxation of the underlying vascular smooth muscle, initiating and maintaining inappropriately increased peripheral and renal vascular resistance. The biochemical steps from oxidative stress to vascular endothelial dysfunction and its detrimental cardiovascular consequences are well established and generally accepted. The unique aspect of our hypothesis resides in the contention that Americans' habitual selection of foods that result in suboptimal dietary intake of potassium and supraphysiological intake of sodium, resulting in oxidative stress of degree in relation to the degree of deviation of potassium and sodium intake from

optimal. Currently Americans consume potassium-to-sodium in molar ratios of less than or close to 1.0 and the IOM recommends a molar ratio of 1.2. Ancestral, pre-agricultural diets, which we physiologically adapted to for 5–7 million years, range from molar ratios of 5.0 to 10.0 or higher. Accordingly, we suggest that the average American is already afflicted with oxidative stress-induced vascular endothelial dysfunction, and therefore the standards for so called normotension and pre-hypertension already reflect a degree of abnormally high blood pressure.

Our hypothesis that dietary imprudence of potassium and sodium is the major environmental cause of essential hypertension through oxidative stress-induced vascular endothelial dysfunction does not exclude other oxidative stress-induced sites and mechanisms to which such dietary imprudence operates to contribute to the etiology of essential hypertension [114]. In particular, we recognize that selection of foods that contain suboptimal amounts of potassium, largely fruits and vegetables, and those foods that contain supraphysiological amounts of sodium, also contain suboptimal amounts of other molecular species that restrict oxidative stress-induced vascular dysfunction (e.g., nitrate, polyphenols), not only affecting hypertension but cardiovascular diseases in general [147-149].

Sources of support

None.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.mehy.2018.08.001.

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