

Review Article

# Mechanism-based strategies to prevent salt sensitivity and salt-induced hypertension

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High-salt diets are a major cause of hypertension and cardiovascular (CV) disease. Many governments are interested in using food salt reduction programs to reduce the risk for salt-induced increases in blood pressure and CV events. It is assumed that reducing the salt concentration of processed foods will substantially reduce mean salt intake in the general population. However, contrary to expectations, reducing the sodium density of nearly all foods consumed in England by 21% had little or no effect on salt intake in the general population. This may be due to the fact that in England, as in other countries including the U.S.A., mean salt intake is already close to the lower normal physiologic limit for mean salt intake of free-living populations. Thus, mechanism-based strategies for preventing salt-induced increases in blood pressure that do not solely depend on reducing salt intake merit attention. It is now recognized that the initiation of salt-induced increases in blood pressure often involves a combination of normal increases in sodium balance, blood volume and cardiac output together with abnormal vascular resistance responses to increased salt intake. Therefore, preventing either the normal increases in sodium balance and cardiac output, or the abnormal vascular resistance responses to salt, can prevent salt-induced increases in blood pressure. Suboptimal nutrient intake is a common cause of the hemodynamic disturbances mediating salt-induced hypertension. Accordingly, efforts to identify and correct the nutrient deficiencies that promote salt sensitivity hold promise for decreasing population risk of salt-induced hypertension without requiring reductions in salt intake.

High-salt diets are estimated to cause approximately one-third of cases of hypertension and at least 1 million deaths per year from cardiovascular (CV) events related to salt-induced increases in blood pressure [1–3]. One approach to preventing salt-induced increases in blood pressure involves regulatory and educational efforts aimed at reducing salt consumption in the general population. This approach holds that in regions like the U.K. and the U.S.A., the amount of salt added to food by industry is a major cause of salt-induced hypertension (Table 1). Based on this view, government regulators are attempting to reduce salt intake in the general population by issuing guidance to the food industry for reducing the amount of sodium added to processed, packaged, and prepared foods [4–6].

**Table 1** Approaches to the problem of salt-induced hypertension

	Regulation-based approach to salt-induced hypertension	Mechanism-based approach to salt-induced hypertension
<b>Cause of the problem</b>	High-salt intake due to the high-salt content of processed foods	Abnormal vascular resistance responses to high-salt intake
<b>Solution to the problem</b>	Reduce salt intake by reducing salt content of processed foods	Correct the mechanisms causing abnormal vascular resistance responses to high-salt intake

Received: 06 February 2022  
Revised: 21 March 2022  
Accepted: 30 March 2022

Version of Record published:  
22 April 2022

A different approach to preventing salt-induced hypertension and CV events involves scientific efforts aimed at correcting the common abnormalities that cause blood pressure-salt sensitivity (sensitivity to the blood pressure effects of high-salt diets) (Table 1). This approach holds that the amount of salt added to food by industry is not the main problem. Rather, an abnormal blood pressure and vascular response to dietary salt (i.e., salt sensitivity) is the problem. Many normal individuals (salt-resistant individuals with normal blood pressure) can consume high-salt diets without developing salt-induced hypertension. Therefore, scientists are interested in identifying and correcting the mechanistic disturbances that cause salt sensitivity (Table 1). This scientific strategy does not require reductions in salt intake. Instead, it is aimed at preventing abnormal blood pressure and vascular responses to dietary salt by converting salt-sensitive individuals to salt-resistant individuals. Here, we discuss why regulatory and educational approaches have had little or no success in reducing salt intake and CV risk in populations like the U.K. over the past 15 years. We then discuss scientific approaches for preventing salt-induced hypertension at the population level that do not depend on reducing salt intake.

## **Reducing intake of sodium chloride versus other forms of dietary sodium**

Government and medical authorities worldwide have long been promoting programs to reduce population intake of sodium [7–9]. Most of the sodium in the diet is in the form of sodium chloride (salt, NaCl) [10,11]. A focus on sodium chloride is relevant because non-chloride sodium salts do not necessarily have adverse effects on blood pressure [12]. For example, compared with sodium chloride, increased intake of sodium citrate appears to have relatively little or no effect on blood pressure [13]. Increased intake of sodium as sodium nitrate may even lower blood pressure [14] or protect against sodium chloride-induced increases in blood pressure [15]. However, some regulatory agencies are interested in reducing the intake of all forms of sodium [6] even though the medical value of reducing consumption of non-chloride sodium salts has not been established. Here we primarily use the term salt (NaCl) because the chloride salt of sodium is largely, if not solely responsible for the influence of dietary sodium on blood pressure.

## **Questioning the value of reducing population salt intake to commonly recommended levels**

Many prominent scientists [16–20] have questioned the presumed benefits of reducing mean population salt intake to levels recommended by various governmental and non-governmental organizations, i.e., levels near or below 5.8 g/day (2.3 g/day sodium) [21–25]. There appears to be consensus that reducing mean salt intake in adults to less than 12.5 g/day (<5 g/day sodium) will reduce CV risk [26]. However, questions have been raised about the benefits of reducing salt intake close to 5.8 g/day or lower [16,17,19,27].

According to Mente and others, mean salt intake of adults in most countries is within a range that is not associated with increased CV risk (7.5–12.5 g/day) (3–5 g/day Na<sup>+</sup>) [20]. The authors contend that this range of salt intake is optimal and that CV disease risk increases when salt intake is above 12.5 g/day (5 g/day sodium) or is below 7.5 g/day (3 g/day sodium) [20]. However, many prominent scientists disagree with this view and advocate regulatory and educational efforts to reduce mean salt intake in the adult population close to or below 5.8 g/day (2.3 g/day sodium) [22,28–31]. Despite the scientific controversy, governments worldwide are moving forward with programs aimed at reducing salt intake close to or below 5.8 g/day (2.3 g/day sodium) [7]. This includes the U.K. and the U.S.A. where mean salt intake is approximately 8.4–8.8 g/day (<3.5 g/day sodium) [32,33].

## **Questioning the feasibility of reducing population salt intake to commonly recommended levels**

In addition to the debate on the risks and benefits of reducing mean population salt intake in most countries, many investigators question the ability of regulatory efforts to reduce population salt intake close to 5.8 g/day [20,34–37]. In contrast, government regulators and others contend that a goal for mean salt intake of 5.8 g/day is achievable in high-income populations such as the U.K. and the U.S.A.—provided that both industry and the public reduce the amount of salt added to food by approximately 40% [38,39]. It is estimated that 75–80% of the salt consumed in European and North American countries comes from processed, packaged, and prepared foods [40,41]. Thus, advocates of population salt reduction argue that to reduce salt intake in such countries, industry must reduce the amount of salt added to food products [42,43]. This raises the question: when industry removes substantial amounts of salt from the food supply in a high-income region like the U.K., what happens to mean salt intake in men and women?

## The failure of food salt reduction to decrease salt intake in England

The U.K. is considered to have pioneered a successful program for reducing the amount of salt added to food by industry [44]. The U.K. Food Standards Agency first published salt reduction targets for industry in March of 2006 [39]. Foods bought in supermarkets were the main targets in the first phase of salt reduction because it was estimated that ‘only ~15% of foods were eaten outside the home’ [43].

According to He and MacGregor, the salt content of most processed foods in the U.K. supermarkets was reduced by 20–30% within 3 years of publication of the salt reduction targets [45]. Proponents of food salt reduction have noted that ‘By getting all companies to work toward the same targets, the United Kingdom has achieved a 20–50% reduction in the salt content of many food products over a decade’ [44]. In addition, Gressier and colleagues reported that between years 2008–2009 and 2016–2017 of the U.K. National Diet and Nutrition Survey (NDNS), sodium density in all foods consumed in the U.K. decreased by 21% (excluding sodium in beverages, fruit juices, and in salt added to food at the table) [46]. A major component of the NDNS program involves systematic monitoring of population salt intake by rigorous measurements of 24-h urine sodium excretion over time. Public Health England (PHE) has performed a comprehensive analysis of the NDNS data to assess the potential impact of food salt reduction on salt intake in the general population [32,47].

Figure 1 (upper panel) shows a plot prepared by PHE of salt intake in men and women in England within the first 10 years of publication of the food salt targets in March of 2006. Simple visual inspection of the data shows little or no change in population salt intake. A trend analysis by PHE showed that in women, there were no significant decreases in mean salt intake at any time after publication of the salt reduction targets (from 2006 to 2019) (Figure 1, lower panel) [32,47]. The lack of a significant change in salt intake in women at any time after introduction of the food salt targets is particularly notable because: (1) the salt intake surveys involved more women than men [32], (2) women were the main target of the public health awareness campaign conducted before, during, and after launch of the food reformulation program [39], and (3) women were significantly more likely than men to be aware of the government guidance to restrict salt intake [48].

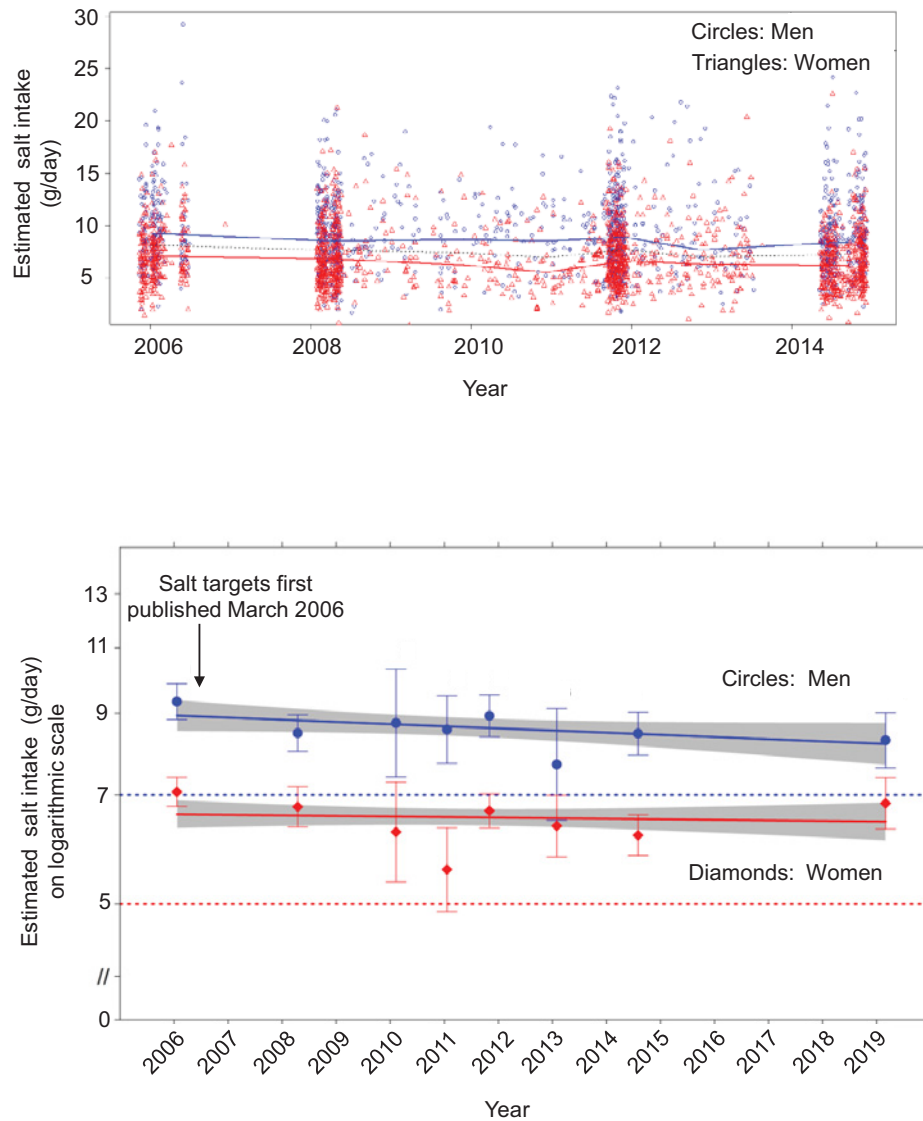
In men, mean salt intake decreased approximately 8% within 3 years of publication of the salt targets without any further significant decrease thereafter (Figure 1, lower panel) [32,47]. Between 2009 and 2017 when sodium density of foods consumed in the U.K. decreased by 21% [46], the PHE analysis shows no significant decrease in salt intake in England [32] (Figure 2, upper panel). Moreover, according to the analysis by PHE [32], there was no statistically significant linear change in general population salt intake over the time between the 2006 publication of the salt reduction targets and the latest salt intake survey completed in 2019 (Figure 2, upper panel). In addition, between 2006 and 2019 in England, there was no significant change in the rate of CV deaths attributable to high intake of sodium (Figure 2, bottom panel) [49]. Despite a 21% reduction in the mean sodium density of foods consumed in the U.K. between 2009 and 2017 [46], there was no significant change in the rate of CV deaths attributable to high-sodium intake in England (Figure 2, bottom panel).

## Overestimating the impact of food salt reduction programs on salt intake

Contrary to the data reported by PHE [32,47], proponents of food reformulation have claimed that salt intake in the general population declined by 15% after publication of the U.K. salt reduction targets [38,50]. As we have discussed elsewhere [36,37], this estimate of 15% is questionable because it: (1) is based on sodium results that were not corrected for method specific analytical bias and (2) involved data on baseline salt consumption (before food reformulation) that PHE deemed inappropriate for use in the trend analysis of salt intake [47].

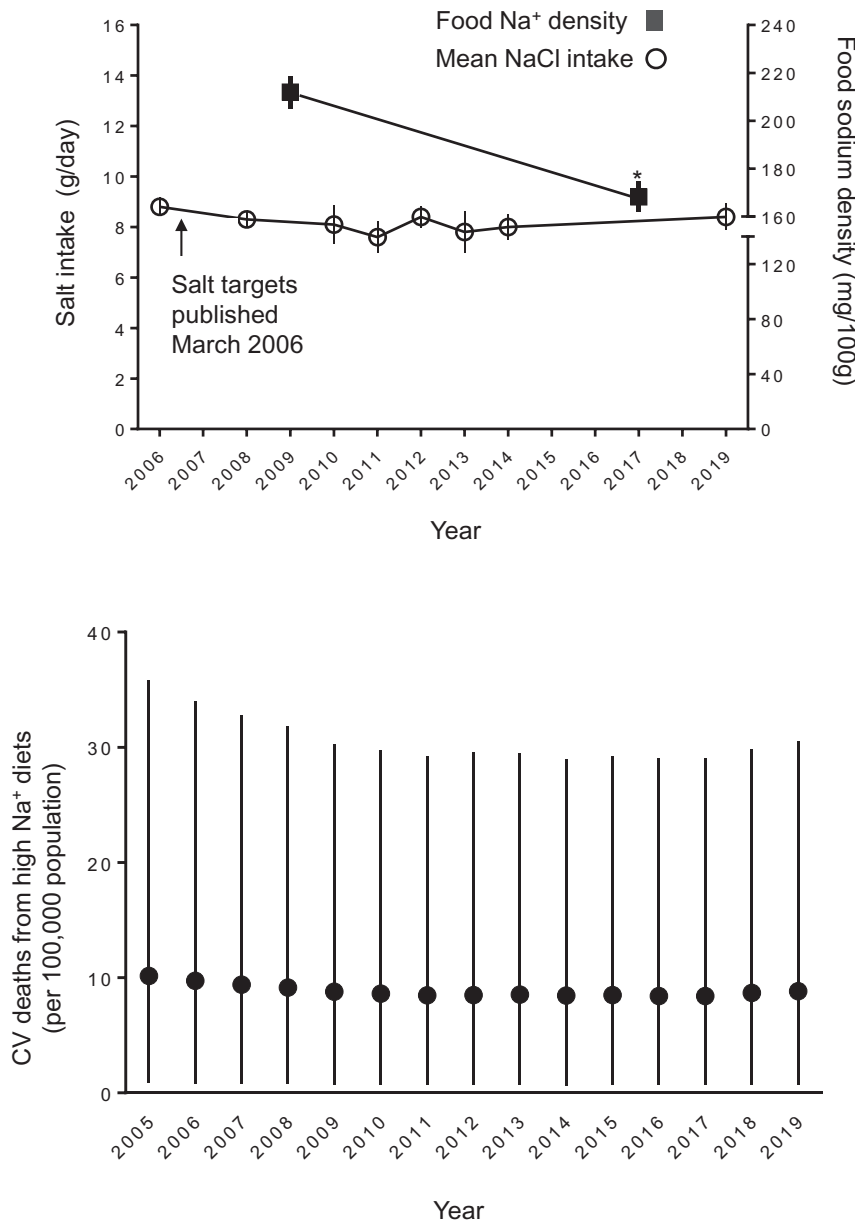
More recently, the same proponents of food reformulation claimed that 5 years after publication of the U.K. salt reduction targets, population salt intake decreased by 10% [51]. However, this claim is also open to question [37] because it is based on a selective analysis of salt intake data from a single year (2011) after publication of the food salt targets. By visualizing the data from all the years (Figures 1 and 2), it is apparent that the lower level of salt intake in 2011 may simply have been due to random variation in estimates of population salt intake over time.

It has been suggested that political meddling in the salt reduction program by the U.K. coalition government formed in 2010 may have interfered with efforts to reduce the amount of salt in the food supply [52]. However, according to Gressier and colleagues, food sodium density significantly decreased by ~20% between years 2008–2009 and 2016–2017 of the NDNS salt intake surveys [46]. Thus, the failure of salt intake to significantly decrease during this



**Figure 1. Analysis by PHE of mean salt intake in England before and after publication of the food salt reduction targets in March 2006**

**Upper panel:** Scatterplots of raw salt intake data from the national nutrition surveys with lines for men (blue line), women (red line), and all [sex-combined adults (black dotted line)] demonstrating relative trends between 2006 and 2014 [47]. The lines pass through the respective geometric means for salt intake from the 2005–2006 survey conducted before publication of the salt targets through completion of the 2014 survey. Details on the graph and the results are available in the PHE report on the 2014 national survey [47]. Note that this figure does not include raw data from the 2019 survey because scatterplots of the raw data were not published in the report on the 2019 survey [32]. **Lower panel:** Mean salt intakes in men and in women in England between 2006 and completion of the most recent national survey in 2019 [32]. Salt intake results are geometric means and 95% confidence intervals for the geometric means. The gray-shaded regions indicate the 95% confidence intervals for the regression lines. The dashed lines indicate the U.K. population target for maximum salt intake in men of 7 g/day and in women of 5 g/day. The change in salt intake for men from 2006 (just before publication of the food salt targets) to 2009 was statistically significant with no significant step change thereafter [32,47]. In women, there was no significant change in salt intake at any time after publication of the salt reduction targets [32]. The slope of the line for salt intake per year over the entire period is not significantly different from zero for men ( $P=0.07$ ; 95% confidence interval  $-1.4$  to  $0.1\%$ ) or for women ( $P=0.61$ ; 95% confidence interval  $-0.8$  to  $0.5\%$ ) [32]. The number of study participants (men and women combined) ranged from 109 to 725 in the different salt intake surveys in England conducted between 2006 and 2019. Details on the survey sample sizes, the graphs, and the statistical analysis are available in the PHE report on the 2019 national survey [32].



**Figure 2. Salt intake data and rates of CV deaths caused by high-salt diets before and after reducing the sodium density of foods consumed in England by ~20%**

**Upper panel:** Trends in population salt intake in England between years 2006 and 2019, and in sodium density of foods consumed in the U.K. between years 2009 and 2017 of the U.K. NDNS (excluding sodium in beverages, fruit juices, and in salt added to food at the table) [46]. Salt intake results are based on measurements of 24-h urine sodium reported in the NDNS surveys [32]. Between 2009 and 2017, mean ( $\pm$  SEM) food sodium density decreased from  $212 \pm 3.4$  to  $168.2 \pm 3.2$  mg/100 g (\*denotes  $P < 0.0001$ ) [46]. This represents a decrease in mean food sodium density of 21% (95% confidence interval of decrease 16, 25%) between 2009 and 2017 [46]. During this period, there was no significant change in mean salt intake in adults in England [32]. Details on sample sizes are reported in [32,46]. **Lower panel:** Rates of CV deaths in England attributed to high-sodium intake from 2005 to 2019. This figure is plotted using data obtained from the Global Burden of Disease (GBD) Study on the health effects of dietary risks where sodium intake was estimated from 24-h urine sodium measurements [2,208]. The GBD investigators defined high-sodium intake as  $>3$  grams/day [2]. The figure shows yearly estimates and 95% uncertainty intervals of the number of CV deaths per 100000 population attributed to high-sodium intake in England. To estimate the impact of sodium intake on CV deaths, the investigators first estimated the relationship between urinary sodium and change in systolic blood pressure, and then estimated the relationship between change in systolic blood pressure and CV death [2].

time as shown in the NDNS report cannot be explained by political meddling in the salt reduction program. Moreover, political meddling cannot explain why salt intake failed to significantly decrease in women between 2006 and 2009 when salt intake appeared to temporarily decrease in men.

## **Why do regulatory efforts that reduce food salt concentration have little or no impact on mean population salt intake in places like the U.K.?**

Salt intake is influenced by complex physiologic pathways [35,53–55]. Based on the work of McCarron and colleagues, it appears that the lower normal physiologic limit for mean population salt intake is approximately 6–7 g/day (~2.3–2.8 g/day sodium) for women and 8–9 g/day ~3–3.5 g/day sodium) for men [35,56]. These mean levels of salt intake are exceeded in approximately 90–95% of populations worldwide. Even in regions where consumption of processed foods is low, the vast majority of free-living populations have a mean salt intake above the range recommended by government and medical organizations of <6 g/day [35,56]. As discussed by McCarron, these observations and others are consistent with salt intake being regulated by human physiology and not by the amount of salt added to processed foods [56].

Given the multiple physiologic factors affecting salt intake [35,53–55], questions have been raised about the ability of government regulators to reduce mean population salt intake below the lower normal physiologic limits [20,35–37,54,56]. In response to reductions in salt content in most of the food supply, individuals may modify their eating habits to maintain salt intake at their physiologically desired limits. This view is consistent with the observation in England that between 2006 and 2019, public health awareness campaigns coupled with substantial reductions in food salt concentration by industry had little or no effect on mean salt intake [32]. The minimal impact of food salt reduction on salt intake in England may be due to the fact that mean salt intake was already close to the lower normal physiologic limit when the salt reduction targets were introduced. In parts of China where processed foods are uncommon, salt consumption is high because consumers add considerable amounts of salt to food at home [57]. In many countries including Brazil, China, Costa Rica, Guatemala, India, Japan, Mozambique, and Romania, more than 50% of salt consumed is obtained from discretionary sources [58]. Clearly, many factors determine salt intake beyond only the amount of salt added to foods by industry. In response to decreases in food salt concentrations, individuals may attempt to satisfy their physiologic desire for salt by eating more foods, consuming a greater proportion of saltier foods, and/or adding more salt to their foods at home. Studies of salt intake in response to reducing salt concentration in only a single type of food [59,60] do not necessarily predict how humans will respond to removal of substantial amounts of salt from the entire food supply.

## **Scientific approaches to preventing salt-induced hypertension that do not depend on reducing salt intake**

Although there is debate over the optimal levels for mean salt intake in the population, there is little or no dispute that in many individuals, large amounts of salt can increase blood pressure and the risk for CV disease [26]. Given the limitations of regulatory and educational efforts to decrease salt consumption in populations like the U.S.A. and the U.K., scientific strategies for preventing salt-induced hypertension that do not require reducing salt intake merit attention. Such strategies are based on correcting the common disturbances that cause blood pressure salt sensitivity.

When properly diagnosed with a validated dietary protocol, blood pressure salt sensitivity is: (1) a highly reproducible phenotype [61] and (2) associated with increased risk for CV events [62]. Most normotensive people are salt resistant (resistant to the pressor effects of high-salt intake) [63,64]. Thus, salt sensitivity is considered an abnormality. Understanding the common determinants of salt resistance and salt sensitivity should facilitate identification of methods for preventing salt-induced hypertension. Specifically, by augmenting the mechanisms involved in protecting against salt-induced increases in blood pressure, it may be possible to convert salt-sensitive individuals into salt-resistant individuals.

## **Changing views on the hemodynamic mechanisms of salt sensitivity and salt resistance**

For decades, it was believed that in normal people (normotensive salt-resistant controls), increases in salt intake cause little or no increase in blood pressure because their kidneys ‘rapidly eliminate the excess salt and blood volume is hardly altered’ [65,66]. Thus, in response to increases in salt intake, it was held that normal people were salt resistant

because they rapidly excreted the salt load and underwent little or no increases in sodium balance, blood volume, and cardiac output [65,67–73].

Consistent with this view of salt resistance, it was widely believed that salt sensitivity was caused by subnormal renal excretion of sodium in response to increases in salt intake [65–67,70,72,74]. According to this historical ‘natriuretic dysfunction’ theory championed by Guyton and others [66,67,70,72,74–79], an impaired renal ability to excrete sodium caused an abnormal increase in cardiac output that initiated and sustained the hypertension. Specifically, it was held that salt-sensitive subjects retained more of a salt load than salt-resistant normal subjects. In salt-sensitive subjects, this greater renal salt retention was said to initiate greater increases in blood volume and cardiac output and thereby initiate greater salt-induced increases in blood pressure [65,70,80]. This theory also held that the increased blood pressure was sustained by persistence of a small increase in cardiac output together with a large elevation in total peripheral resistance occurring secondary to the process of ‘whole-body autoregulation’ of blood flow [65,67,69,81]. According to this theory, the elevated total peripheral resistance and hypertension could not be sustained without persistence of a slightly increased cardiac output [65,67,69,81]. The small increase in cardiac output required to sustain the hypertension was said to be so small that it could not be detected with any known methods of measurement [67,68]. Based on these historical views, efforts to prevent salt-induced hypertension have traditionally focused on developing methods to prevent the abnormally elevated cardiac output by either: (1) reducing salt intake or (2) increasing renal salt excretion.

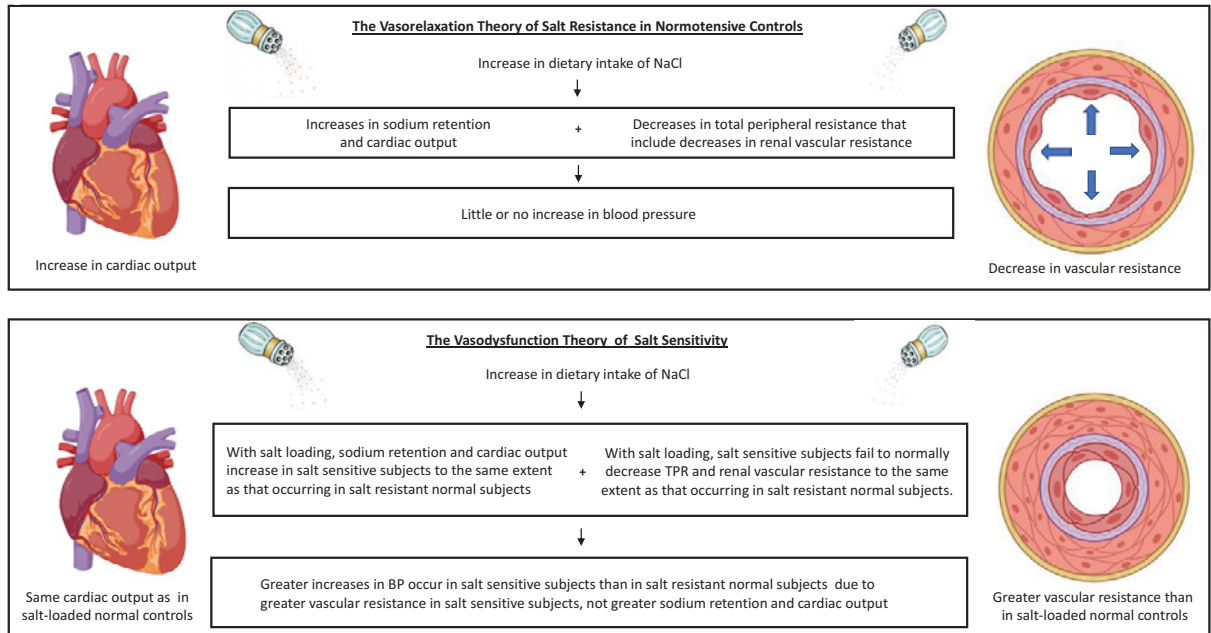
As we have discussed in detail elsewhere [63,82,83], these historical views on mechanisms of salt sensitivity and salt resistance were based on early studies that lacked measurements of sodium balance during salt loading in normal controls (salt-resistant normotensive subjects) [68,75,84–89]. Later studies in humans and animals demonstrated that in response to increases in salt intake, salt-resistant normal controls usually retain large amounts of sodium—just as much sodium retained by salt-sensitive subjects [90–97]. Recently, the traditional Guyton model which holds that salt-resistant normal subjects rapidly excrete a salt load and retain little sodium was directly investigated and failed validation testing [98,99].

Newer theories for the usual hemodynamic mechanisms of salt resistance and salt sensitivity have emerged that better explain the different blood pressure responses to salt loading in salt-sensitive humans versus salt-resistant normal controls. These contemporary theories for salt resistance (‘vasorelaxation’ theory) [63,100] and salt sensitivity (‘vasodysfunction’ theory) [82,83], have implications for developing new approaches to preventing salt-induced hypertension that do not depend on restricting salt intake (Figure 3).

## The vasorelaxation theory of salt resistance and the vasodysfunction theory of salt sensitivity

In many normal humans and animals (normotensive salt-resistant controls), a common response to salt loading involves: (1) substantial increases in sodium balance and cardiac output, together with (2) vasodilation and decreases in total peripheral resistance (systemic vascular resistance) that include the renal vasculature (Figure 3, upper panel) [63,83,101–104]. In normal individuals, salt loading often does not increase blood pressure much because the vasodilation and reductions in vascular resistance offset the potential pressor effects of salt-induced increases in sodium balance and cardiac output (Figure 3, upper panel) [63,83]. The reductions in renal vascular resistance contribute to the reductions in systemic vascular resistance but do not cause normal subjects to excrete more sodium and retain less of it than salt-sensitive subjects [83]. This vasorelaxation theory of salt resistance appears to explain why increases in salt intake have little or no effect on blood pressure in many if not most normotensive individuals (Figure 3, upper panel) [100]. Note that the vasorelaxation theory does not exclude the possibility that in some normal individuals, salt resistance might be mediated by mechanisms that limit increases in cardiac output or even cause decreases in cardiac output in response to increases in salt intake. For example, in some cases, increases in salt intake might conceivably cause increases in vascular resistance associated with decreases in cardiac output and therefore no changes in blood pressure. However, the most common hemodynamic pattern observed in the few studies conducted to date fits the sequence of events described by the vasorelaxation theory (Figure 3, upper panel).

According to the vasodysfunction theory of salt sensitivity, salt-induced increases in blood pressure are often initiated by: (1) a failure to normally vasodilate and decrease vascular resistance in response to salt loading, together with (2) normal increases in sodium balance and cardiac output in response to salt loading (Figure 3, lower panel) [82,83]. The abnormal vascular resistance response to salt loading includes the renal vasculature and also portions of the extrarenal vasculature [83,103,105–109]. In salt-sensitive subjects, renal vascular resistance fails to decrease to a normal extent and actually increases above baseline [83,103,105–109]. The abnormal renal vascular resistance response to increases in salt intake may constrain salt-sensitive subjects from excreting more salt than is ingested.



**Figure 3. Contemporary theories of the hemodynamic mechanisms often mediating salt resistance and salt sensitivity**

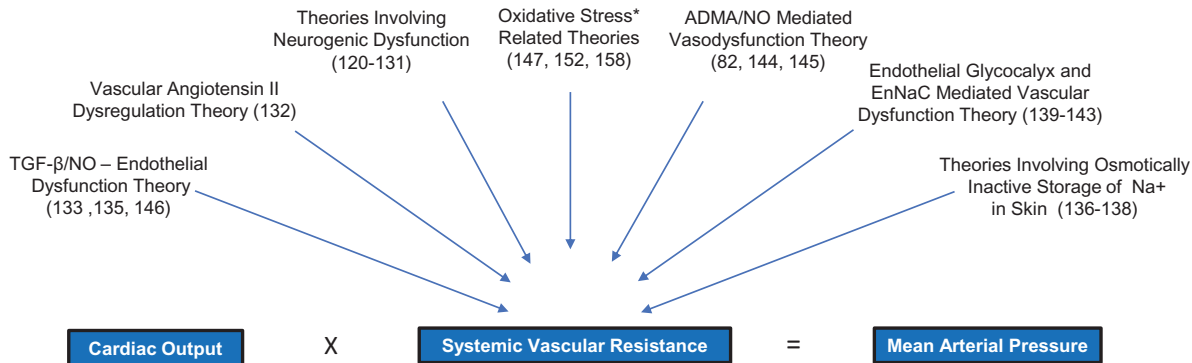
**Upper panel:** The vasorelaxation theory of salt resistance in normal individuals. The sodium balance and hemodynamic responses to increased salt intake shown here are based on the results of multiple short-term, salt-loading studies in salt-resistant humans and animals with normal blood pressure [63,82,90,91,93–97,209–220]. Abbreviation: TPR, total peripheral resistance. Figure adapted from [100]. **Lower panel:** The vasodysfunction theory of salt sensitivity. The sodium balance and hemodynamic responses to increased salt intake shown here are based on the results of multiple short-term salt-loading studies in which salt-sensitive humans and animals have been compared with salt-loaded normal controls (salt-resistant subjects with normal blood pressure) [63,82,90,91,93–97,210,212,214,215,221]. Figure adapted from [100] and created with BioRender.com. Abbreviations: SR, salt-resistant; SS, salt-sensitive; TPR, total peripheral resistance.

However, it does not cause salt-sensitive subjects to retain more of a sodium load than salt-resistant normal subjects. Thus, in humans, the initiation of salt-induced increases in blood pressure often involves the combination of (1) abnormal vascular resistance responses to salt loading that cause total peripheral resistance (including renal vascular resistance) to become greater in salt-sensitive subjects than in salt-resistant normal controls, and (2) normal increases in renal sodium retention that do not cause greater increases in sodium balance and cardiac output in salt-sensitive subjects than in salt-resistant normal controls.

## A vasoconstriction theory of salt sensitivity

It has been reported that in some cases of salt-induced hypertension, increases in blood pressure are initiated by increases in vascular resistance in the absence of increases in cardiac output or even with decreases in cardiac output. For example, Obst and colleagues studied unilaterally nephrectomized mice during induction of hypertension by subcutaneous administration of deoxycorticosterone acetate (DOCA) and provision of a 1% NaCl solution to drink [110]. Cardiac output measured with a Doppler flow probe around the ascending aorta did not increase during induction of the DOCA-NaCl hypertension [110]. In studies of the initiation of mineralocorticoid-induced hypertension in dogs, pigs, and sheep, the hemodynamic pattern has been variable. In some animals, the hemodynamic pattern in response to salt loading is consistent with the vasodysfunction theory (Figure 3, bottom panel) [111–115]. In other animals, the induction of salt-dependent hypertension is better explained by a vasoconstriction theory in which the increases in blood pressure are initiated by increases in vascular resistance with little or no increase in cardiac output or even a decrease in cardiac output [113–116]. These studies provide no evidence for the historical theory of salt sensitivity that initiation of salt-induced increases in blood pressure requires abnormally large increases in cardiac output [66,67,75,76]. In addition, recent studies challenge the concept that salt-dependent hypertension is sustained





**Figure 4. Examples of contemporary theories on mechanistic abnormalities causing salt sensitivity**

These contemporary theories on the mechanistic disturbances that can cause salt sensitivity fit within the unifying conceptual framework shown in Figure 3. These theories do not depend on the assumption that in response to increases in salt intake, salt-sensitive individuals usually undergo greater increases in sodium retention and cardiac output than salt-resistant normotensive controls.

\*Note that oxidative stress has been proposed to play a role in many of the theories of salt-sensitivity listed here. Abbreviations: ADMA, asymmetrical dimethylarginine; ENaC, epithelial sodium channel; ENaC, endothelial ENaC; TGF-β, transforming growth factor-β.

by increases in cardiac output that are too small to be detected [67,69,79,117]. For example, in studies by Ball and colleagues in which blood pressure was increased by administration of aldosterone and a high-salt diet, cardiac output was found to be decreased in the established phase of hypertension [118].

## Mechanism-based approaches to prevent salt-induced hypertension

According to the vasodysfunction theory, the induction of salt-induced hypertension often involves the combination of normal salt-induced increases in sodium balance and cardiac output (similar to those observed in normal salt-resistant controls) together with subnormal vasodilation and abnormal levels of vascular resistance (Figure 3, bottom panel). In such cases, initiation of salt-induced hypertension could be prevented by either (1) preventing the abnormal vascular resistance responses to increases in salt intake (preventing vasodysfunction) or, (2) preventing the normal increases in sodium balance and cardiac output induced by increases in salt intake.

We suggest that interventions to prevent salt-induced hypertension primarily focus on preventing the abnormal physiologic mechanisms that appear to commonly mediate salt sensitivity, i.e., preventing the abnormal vascular resistance responses to salt loading that are usually required for initiation of salt-induced increases in blood pressure [119]. This raises the related questions: (1) in normal salt-resistant humans, what are the common mechanisms that mediate vasodilation and decreases in vascular resistance in response to increases in salt intake and (2) in salt-sensitive humans with normal blood pressure, what are the common mechanisms mediating the failure to normally vasodilate and reduce vascular resistance in response to increases in salt intake (vasodysfunction)?

## Mechanisms of vasorelaxation and vasodysfunction in response to increases in salt intake—a focus on nitric oxide

In normotensive salt-resistant controls, normal vasorelaxation in response to increases in salt intake could be mediated by decreased activity of vasoconstrictor pathways or by increased activity of vasodilator pathways or both. In salt-sensitive subjects, the failure to normally vasodilate and decrease vascular resistance in response to increases in salt intake could be mediated by abnormally high activity of vasoconstrictor pathways or abnormally low activity of vasodilator pathways or both. Figure 4 shows many contemporary theories on the pathogenesis of salt sensitivity that involve pathways influencing vascular resistance [82,120–147]. These theories do not depend on the questionable assumption that salt-sensitive humans usually excrete a salt load more slowly than normal controls. Given that salt resistance often involves decreases in vascular resistance in response to increases in salt intake, the role of the potent vasodilator nitric oxide (NO) in mediating blood pressure responses to high-salt diets is of considerable interest [148].

It has been proposed that increases in salt intake normally cause increases in blood volume, cardiac output, and blood flow that result in shear stress-mediated release of NO from endothelial cells leading to vasodilation and decreases in vascular resistance [104]. Over 30 years ago, the seminal studies of Chen and Sanders showed that in the classic Dahl rat model of salt sensitivity, disturbances in NO activity can play a major role in the pathogenesis of salt-induced hypertension [149]. Subsequently, studies by many other investigators in salt-sensitive humans and animals indicated that impaired vasodilator responses to salt loading often involve a reduced ability to increase NO activity in response to increases in salt intake [82,93,144,145,148–154]. In humans and in animal models, increases in oxidative stress and in the activity of asymmetrical dimethylarginine (ADMA), an endogenous inhibitor of NO synthase activity, have been implicated in mediating impaired NO activity in response to increases in salt intake [93,144,145,148,152–160]. Although disturbances in other pathways (e.g. neural pathways) (Figure 4) can also mediate abnormal vascular resistance responses to changes in salt intake, we are particularly interested in NO-related pathways because of their potential to be manipulated by non-pharmacologic means.

## Promoting salt resistance by non-pharmacologic manipulation of NO activity

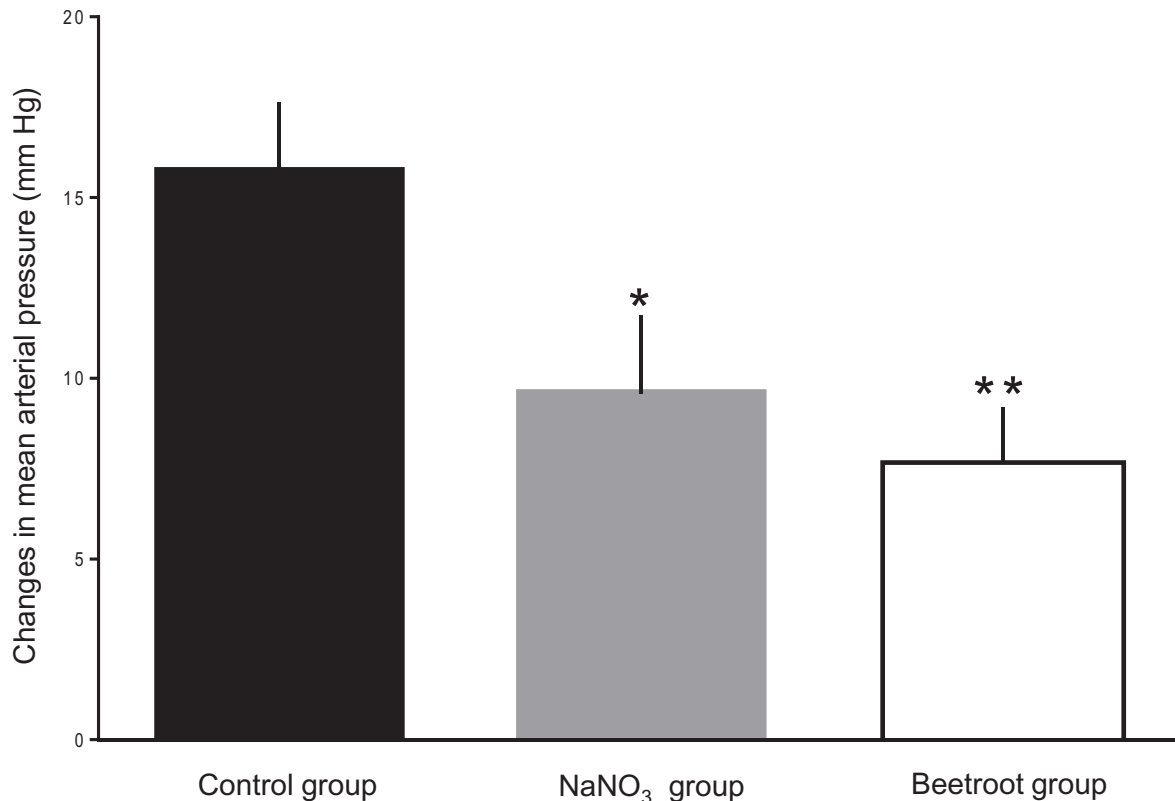
In 1991, Chen and Sanders reported that administration of large amounts of L-arginine, the substrate for enzymatic generation of NO by NO synthase in the classical NO production pathway, could prevent salt-induced hypertension in Dahl salt-sensitive rats [149]. Subsequent studies indicated that in normotensive humans consuming low normal amounts of arginine, substantial increases in dietary intake of L-arginine could reduce blood pressure [161]. However, large amounts of arginine are required to influence blood pressure and patients with endothelial dysfunction may have an impaired ability to convert L-arginine into NO. The use of arginine supplements to prevent hypertension and CV disease in the general population has practical limitations and may also have adverse effects in some patient subgroups [162].

An alternative pathway for augmenting NO activity that does not depend on enzymatic generation of NO from L-arginine involves the stepwise reduction in dietary nitrate to nitrite to NO [163,164]. Many investigators have proposed that increasing intake of nitrate-rich vegetables like beetroot can safely modulate blood pressure by increasing NO activity through this alternate pathway [165–169]. In randomized, double blind, placebo-controlled studies in humans, administration of supplemental nitrate in the form of sodium nitrate or beetroot juice has been reported to reduce blood pressure [14,170]. However, the amounts of nitrate provided were considerable and the practical implications of these observations for preventing salt-induced hypertension in the general population are unclear.

## Preventing salt-induced hypertension by fortifying salty foods with nitrate-rich vegetable extracts

In contrast with the large amounts of sodium nitrate or beetroot required to lower blood pressure, we have found that tiny amounts of inorganic nitrate in the form of sodium nitrate or beetroot juice can protect against initiation of salt-induced increases in blood pressure [15]. In the most widely used animal model of spontaneous salt sensitivity, the Dahl salt-sensitive rat, we found that providing a molar ratio of added nitrate to added salt of <1:100 conferred substantial protection against salt-induced increases in blood pressure [15] (Figure 5). The findings indicate that on a molar basis and a weight basis, dietary nitrate may be ~100-times more potent than dietary potassium with respect to providing substantial resistance to the pressor effects of increased salt intake [15]. Although small amounts of nitrate were not sufficient to reverse hypertension, they were remarkably effective in attenuating the initiation of salt-induced increases in blood pressure. These observations have opened up the possibility of safely preventing salt-induced hypertension by fortifying salty foods with small amounts of nitrate-rich vegetable extracts. In humans, the amounts of added nitrate required for protecting against salt-induced increases in blood pressure would be well below the World Health Organization (WHO) limit for the acceptable daily intake of nitrate (~262 mg/day for a 70 kg human), and the reference dose for nitrate set by the U.S. Environmental Protection Agency (~490 mg/day for a 70 kg human) [171–173].

In addition to nitrate, it should be noted that certain vegetables including beetroot may contain other substances influencing blood pressure such as flavonoids, phenolic acids and amides, carotenoids, betacyanin, betaxanthin, ascorbic acid, and potassium [174]. This raises the possibility that some vegetable extracts might have greater capacity to attenuate salt-induced hypertension than administration of nitrate salts alone.



**Figure 5. Effects of small amounts of supplemental sodium nitrate or beetroot on salt-induced increases in blood pressure in Dahl salt-sensitive rats**

Oral administration of supplemental nitrate in the form of sodium nitrate or beetroot juice containing inorganic nitrate afforded significant protection against salt-induced increases in blood pressure. The figure shows salt-induced changes in mean arterial pressure determined by 24-h radiotelemetric measurements of blood pressure. Statistical significance was determined by ANOVA with Holm–Sidak testing to adjust for multiple comparisons. \* denotes adjusted  $P < 0.05$  compared with the salt-loaded control group. \*\* denotes adjusted  $P < 0.025$  compared with the salt-loaded control group. The salt-induced changes in mean arterial pressure were  $15.7 \pm 1.9$  mmHg in the control group ( $n=7$ ),  $9.5 \pm 2.1$  mmHg in the sodium nitrate group ( $n=7$ ), and  $7.6 \pm 1.5$  mmHg in the beetroot group ( $n=6$ ). Figure adapted from [15].

## Preventing salt sensitivity by increasing potassium intake

A potassium intake of approximately 3500 mg/day is recommended for adults by the WHO and the U.K. National Health Service (NHS) [175,176]. Salt sensitivity has been demonstrated in normotensive individuals consuming less than this recommended amount of potassium [153,177]. In these individuals, salt-induced increases in blood pressure were prevented by specifically increasing potassium intake above 3500 mg/day (3900–4700 mg/day) with potassium bicarbonate or potassium chloride [153,177]. Thus, augmenting potassium intake represents an additional strategy for reducing the risk for salt-induced hypertension that does not require a reduction in salt intake. It should also be noted that the greater salt sensitivity in adults self-identified as black compared with those self-identified as white may be related to lower potassium consumption in black individuals [178]. The racial disparity in salt sensitivity is reduced or eliminated when potassium intake is near or above the amount recommended by the NHS and the WHO [178]. It appears that supplemental potassium may protect against salt-sensitivity by augmenting renal excretion of sodium [177] and also by influencing NO activity and vascular resistance responses to increases in salt intake [153,179].

Supplemental potassium intake can also reduce blood pressure. The blood pressure-lowering effects of high-potassium intake appear to be greater at higher levels of salt intake [180]. For example, in individuals consuming considerable amounts of salt (7 g/day of salt or more), achieving potassium intakes of approximately 3500

mg/day or more reduced blood pressure in the absence of a reduction in salt intake [181–185]. In studies in individuals consuming low-salt diets (<4.8 g/day), achieving potassium intakes above 3500 mg/day (~3500–5000 mg/day) did not reduce blood pressure [186,187]. As noted by Drewnowski and others, independently increasing potassium intake without reducing salt intake may have beneficial effects on health [188,189].

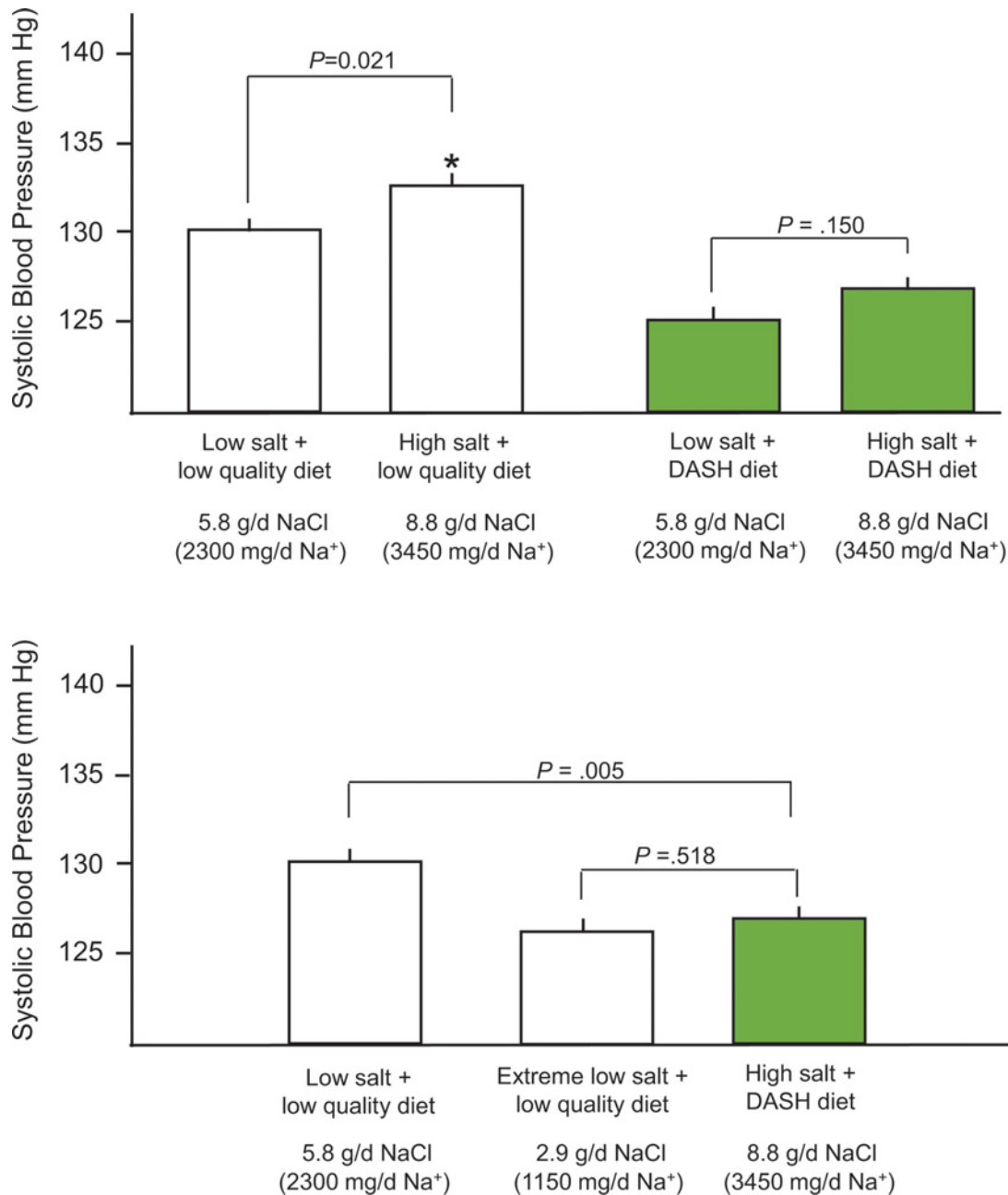
Given the favorable blood pressure effects of supplemental potassium intake in individuals consuming high-salt diets, various government and medical authorities are engaged in educational efforts to promote greater potassium consumption in the general population. However, efforts to increase potassium consumption by encouraging greater intake of fruits and vegetables have met with little success. Median potassium intakes in the U.K. and the U.S.A. remain far below the level recommended by the NHS and the WHO [188]. Thus, there is ongoing interest in methods to augment potassium intake that do not depend on increasing intake of fruits and vegetables. One such method is the use of salt substitutes prepared by adding potassium chloride to sodium chloride.

## Potassium-enriched salt substitutes

Salt substitutes are often prepared by mixing potassium chloride with sodium chloride and thus have lower sodium chloride content and greater potassium content than regular salt. Potassium chloride has a bitter or metallic taste which might limit consumer acceptance of salt substitutes [190]. However, it is reported that most individuals cannot distinguish between regular salt and salt substitutes containing no more than 30% potassium chloride [191]. Use of potassium-enriched salt substitutes in place of regular salt increases potassium intake and decreases salt intake and can significantly reduce blood pressure [191]. For example, in a cluster-randomized trial in rural China of study participants consuming large amounts of salt (10.8 g/day) and a potassium-deficient diet (1400 mg/day), use of a salt substitute (25% KCl + 75% NaCl) reduced salt intake by almost 1000 mg/day and increased potassium intake by almost 1000 mg/day (adjusted for the changes that occurred in control subjects not using the salt substitute) [192]. Importantly, these changes in salt intake and potassium intake were associated with a significant reduction in systolic blood pressure of  $-3.3$  mm Hg (95% CI  $-4.5$  to  $-2.2$ ) [192]. During use of the salt substitute, salt consumption and potassium consumption remained far from recommended levels. Nevertheless, in the study participants using the salt substitute, the rates for stroke and for death were significantly reduced by approximately 4–5 events per 1000 patient years [192]. There was no evidence of increased risk of hyperkalemic events in the group receiving the salt substitute. The relative contributions of potassium supplementation versus reduced salt intake to the improved outcomes was not determined. With use of the salt substitute, the relative increase in total potassium intake was much greater than the relative decrease in total salt intake. These findings demonstrate the potential for salt substitutes to reduce blood pressure and decrease rates of stroke and death in people consuming large amounts of salt and low amounts of potassium. Given that higher potassium intakes can prevent or reduce salt-induced increases in blood pressure [153,177], it is possible that potassium supplementation itself could reduce CV mortality even in the absence of a reduction in salt intake.

## Suboptimal nutrient intake—a common cause of salt sensitivity

Excess intake of refined carbohydrates such as fructose may increase risk for salt-induced increases in blood pressure [193]. While dietary excesses and obesity can play a role in salt sensitivity [194], here we focus on dietary deficiencies as determinants of salt sensitivity. The impact of low-potassium intake on risk for salt sensitivity highlights the role of deficient nutrient intake in the pathogenesis of salt-induced increases in blood pressure [153,177,195]. It is now well established that augmenting intake of various nutrients can promote salt resistance [153,177,178,196]. Accordingly, salt sensitivity may be viewed as a problem of deficient nutrient intake—not just a problem of excessive intake of salt and other dietary components. The best evidence for this comes from the Dietary Approaches to Stop Hypertension (DASH) DASH-Na<sup>+</sup> trial [196]. In the DASH-Na<sup>+</sup> trial, salt sensitivity was observed when study participants were fed a ‘control’ diet that provided much lower amounts of potassium, magnesium, calcium, and nitrate than the average amounts consumed in the U.K. and the U.S.A. [196–198] (Figure 6, upper panel). In normotensive or hypertensive study participants consuming this below average ‘control’ diet, increasing salt intake from the widely recommended level of 5.8 g/day (2300 mg/day Na<sup>+</sup>) up to a level of 8.8 g/day (3500 mg/day Na<sup>+</sup>) significantly increased systolic blood pressure (Figure 6, upper panel) [199]. In contrast, the study subjects consuming the DASH diet rich in potassium, nitrate and other nutrients were protected from salt-induced increases in blood pressure. In individuals consuming the DASH diet, increasing salt intake from the recommended level of 5.8 g/day (2300 mg/day Na<sup>+</sup>) up to the level of 8.8 g/day (3500 mg/day Na<sup>+</sup>) did not significantly increase blood pressure (Figure 6, upper panel) [196].



**Figure 6. Effects of the DASH diet on the blood pressure responses to changes in salt intake**

**Upper panel left (open bars).** In subjects consuming a low-quality diet ( $n=204$ ) that delivered the low amount of salt recommended by the U.K. and U.S.A. (~5.8 g/day), increasing salt intake to 8.8 g/day for 4 weeks significantly increased systolic blood pressure (mean change of 2.7 mmHg with 95% CI, 0.3–5.0) [222]. **Upper panel right (solid bars).** In subjects consuming the DASH diet ( $n=208$ ) that delivered the low amount of salt recommended by the U.K. and U.S.A. (~5.8 g/day), increasing salt intake to 8.8 g/day for 4 weeks did not significantly increase systolic blood pressure (mean change of 1.6 mmHg with 95% CI, –0.7 to 3.8) [222]. **Lower panel.** Systolic blood pressure is significantly lower in subjects consuming the DASH diet ( $n=208$ ) and a large amount of salt (8.8 g/day) for 4 weeks than in subjects consuming the low-quality diet ( $n=204$ ) and a low amount of salt typically recommended by the U.K. and U.S.A. health authorities (5.8 g/day). Systolic blood pressure in subjects consuming the DASH diet and a large amount of salt (8.8 g/day) for 4 weeks is just as low as in subjects consuming the low-quality diet and an extremely low amount of dietary salt not recommended by the U.K. and U.S.A. health authorities (2.9 g/day). All of the graphs in these figures were drawn using DASH study data reported in [222]. The statistical analysis of the results in the upper panels is provided in [222]. The statistical analysis of the results in the lower panel is based on ANOVA with Holm-Sidak testing to adjust for multiple comparisons using data from reference [222].

## Salt restriction is not necessary for the blood pressure-lowering effects of the DASH diet

In study participants consuming a large amount of salt (8.8 g/day), consumption of the DASH diet reduced blood pressure to the same level achieved by extreme salt restriction (2.9 g/day NaCl, 1150 mg/day Na<sup>+</sup>) in study subjects consuming the low quality ‘control’ diet (Figure 6, lower panel) [196,199]. It should be noted that this extremely low level of sodium intake of 1150 mg/day is well below the adequate intake (AI) level for sodium in adults set by the National Academy of Sciences, Engineering, and Medicine (NASEM) in the U.S. (AI = 1500 mg Na<sup>+</sup>/day) [200] and by the European Food Safety Authority (EFSA) (AI = 2000 mg Na<sup>+</sup>/day) [201]. Although severe salt restriction to 2.9 g/day (1150 mg Na<sup>+</sup>/day) can also reduce blood pressure in people consuming the DASH diet [196], this is not recommended or feasible in general clinical practice. Notably, salt restriction to the levels generally recommended by medical and government authorities (5.8 g/day NaCl, 2300 mg/day Na<sup>+</sup>) did not significantly enhance the blood pressure-lowering effects of the DASH diet [196,199]. Thus, when switching to the DASH diet in individuals consuming the average amount of salt consumed in the U.S.A. or the U.K., there is no added blood pressure benefit of reducing salt intake to the level of 5.8 g/day (2300 mg Na<sup>+</sup>/day) recommended by many government and medical authorities.

The DASH Na<sup>+</sup> trial demonstrates that by increasing intake of multiple dietary constituents, salt-induced increases in blood pressure can be prevented without reducing salt intake (Figure 5). Furthermore, the DASH diet consistently lowers blood pressure across a diverse range of individuals [202]. However, adherence to the DASH diet is poor and further research is needed on methods for increasing use of the DASH diet in the general population [202,203].

## What nutrients mediate the ability of the DASH diet to prevent salt sensitivity?

It is unknown which particular components of the DASH diet corrected the salt sensitivity and were largely responsible for preventing salt-induced increases in blood pressure. Compared with the control diet, the DASH diet contained much greater amounts of fiber in addition to greater amounts of potassium, magnesium, calcium, and nitrate [196]. It also limits saturated fat and sugar. For example, the original DASH diet provides approximately 1.5–3-fold more nitrate (160 mg/day) [204] than the average amounts of nitrate consumed in the U.K. and the U.S.A. [205]. The DASH diet also provides approximately 1.9-fold more potassium than the average amount consumed in the U.K. and the U.S.A.) [200,206]. Research by Al-Solaiman and colleagues suggests that the blood pressure-lowering effects of the DASH diet are not simply due to the amounts of potassium, magnesium, or fiber in the diet [207]. However, further studies are required to determine the relative contributions of various nutrients in the DASH diet to protection from salt-induced increases in blood pressure.

### Summary

Over the past 15 years in the U.K. and the U.S.A., regulatory and educational efforts to reduce salt intake and the risk for salt-induced hypertension and CV disease have met with little success. Reducing the sodium density of all foods consumed in the U.K. by 21% (excluding beverages, fruit drinks, and added table salt) had little or no impact on population salt intake in England. These observations should motivate the investigation of mechanism-based strategies for preventing salt-induced increases in blood pressure that do not depend on reducing salt intake. Most normotensive people are resistant to salt-induced increases in blood pressure and blood pressure-salt sensitivity is considered an abnormality. Thus, there is growing interest in preventing the underlying disturbances that cause salt sensitivity in the first place. Salt sensitivity is now recognized as a problem that is often caused by suboptimal nutrient consumption that promotes abnormal vascular resistance responses to high-salt diets. In humans and in animal models, optimizing nutrient intake can prevent salt-induced increases in blood pressure. Accordingly, there is ongoing interest in identifying the most effective nutrients for promoting salt resistance and developing ways to augment consumption of those nutrients in the general population. Potassium-enriched salt substitutes and fortification of salty foods with nitrate-rich vegetable extracts are examples of potential methods for preventing salt-induced hypertension that do not depend on restricting salt intake to levels recommended by various regulatory authorities.

## Competing Interests

The authors declare the following potential competing interests:

Michal Pravenec and Stephen E. DiCarlo have nothing to disclose. Theodore W. Kurtz is a co-founder and stockholder of Mission Salt, Inc, that has filed patents for salty food compositions including nitrate-rich vegetable ingredients. The company's goal is to develop methods to prevent salt-induced hypertension. Theodore W. Kurtz did not receive any financial support from Mission Salt and no funds from Mission Salt were used for the submitted work.

## Funding

This work was supported by the Praemium Academiae award of the Czech Academy Sciences [grant number AP1502 (to Michal Pravenec)].

## Open Access

Open access for this article was enabled through a transformative open access agreement between Portland Press and the University of California.

## Abbreviations

AI, adequate intake; CV, cardiovascular; DASH, Dietary Approaches to Stop Hypertension; DOCA, deoxycorticosterone acetate; NDNNS, National Diet and Nutrition Survey; NHS, National Health Service; NO, nitric oxide; PHE, Public Health England; WHO, World Health Organization.

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