**Special Article**

**Salt sensitive hypertension: mechanisms and effects of dietary and other lifestyle factors**

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Salt sensitivity, the difference in blood pressure response to high salt intake, is an independent cardiovascular and mortality risk factor. It is associated with physiological, environmental, demographic, and genetic factors. This review focuses on physiological mechanisms of salt sensitivity in populations at particular risk and the associated dietary factors. Interplay of mechanisms such as the renin-angiotensin aldosterone system, endothelial dysfunction, ion transport and oestrogen decrease in women is contributing to development of salt sensitivity. Due to their effects on these systems, higher dietary intakes of potassium, calcium, vitamin D, antioxidant vitamins, proteins rich in l-arginine, and adherence to dietary patterns similar to DASH can be beneficial to salt-sensitive populations. In contrast, diets similar to typical Western diet, rich in saturated fats, sucrose and fructose together with excessive alcohol consumption may exacerbate salt-sensitive changes in BP. Identifying potential mechanisms of salt sensitivity in susceptible populations and linking it to protective or harmful dietary and lifestyle factors can lead to more specific guidelines towards prevention of hypertension and cardiovascular diseases.

**Key words: salt sensitivity, diet, hypertension, blood pressure**

**INTRODUCTION**

Hypertension is one of the leading causes of cardiovascular diseases (CVD) worldwide and is strongly related to vascular and overall mortality.1 It is largely a modifiable risk factor with dietary salt being one of the main contributors. The link between dietary salt intake and hypertension is well established and it has been shown that a reduction in salt intake lowers blood pressure (BP).2,3 However, it has also been noted that individuals’ BP responds differently to dietary salt intake, with some exhibiting an increase in BP with increasing dietary salt, while in others no significant difference in BP is observed.4This phenomenon is called salt sensitivity. There are a number of definitions and methods for determining salt sensitivity with one of the major concerns being the reproducibility of the method used.5 In earlier studies conducted by Weinberger and his group,4 a quick protocol was used with patients being given a saline infusion on one day and restricted sodium intake and oral diuretic the second day. Patients exhibiting a fall in mean arterial pressure (MAP) of more than 10mmHg were considered to be salt-sensitive and ones with a fall of less than 5 mmHg as salt-resistant. More recent research suggests a dietary method whereby individuals are placed on a low salt diet followed by a high salt diet. Specifically, individuals receive a low sodium diet (3 grams of salt or 51.3 mmol of sodium per day) for seven days. Afterwards they receive a high sodium diet (18 grams of salt or 307.8 mmol of sodium per day) for an additional seven days. Patients are then classified as salt-sensitive or salt-resistant according to changes in their BP from low- to high salt periods. This dietary method is reproducible and has been adopted by the majority of researchers as the most reliable to date.6,7Even though salt sensitivity is more often expressed as a categorical variable, some investigators have expressed salt sensitivity as a continuous variable representing the change in BP in response to dietary salt (ΔBP).8 Considering the discrepancy in the methods used by different researchers, determining the prevalence of this phenomenon is problematic. Nevertheless, Weinberger et al.4 have estimated salt sensitivity to be present in 51% of hypertensive and 26% of normotensive population with the incidence of hypertension being higher in salt-sensitive individuals than in salt-resistant individuals.9 Moreover, salt sensitivity is considered to be an independent cardiovascular and mortality risk factor. Normotensive adult salt-sensitive individuals have a cumulative mortality rate similar to that of hypertensive ones, whereas salt-resistant normotensive individuals have an increased survival rate.10 As a complex phenomenon, salt sensitivity is associated with numerous physiological, environmental, genetic, and demographic factors.11,12 Strong demographic predictors of salt sensitivity are sex, race and age.13,11 Research conducted to date has shown that postmenopausal women, black and older populations are the groups with higher risk of developing salt sensitivity.14,15 Biological background of salt sensitivity is complex and not entirely elucidated.16,17 Moreover, research to date has shown that besides dietary sodium, the most important environmental contributor, other dietary factors play an important role in development and prevention of salt sensitivity.18,19 Considering its impact on overall health, the aim of this review is to identify the possible mechanisms of salt sensitivity in populations at particular risk, together with dietary and lifestyle factors that may act protective or harmful by influencing these systems. This can lead to development of more successful therapeutic approaches in cardiovascular and overall health. Research conducted to date on this topic will be presented in three sections. First section will present the most prominent physiological mechanisms that may be related to salt sensitivity in black, older populations and postmenopausal women. Genetic predisposition in blacks will also be explained. This will be followed by the research on micronutrients and macronutrients affecting these mechanisms. Lastly, the research on dietary and lifestyle factors related to salt sensitivity will be presented. Mechanisms of their action are yet to be explored.

**PHYSIOLOGICAL MECHANSIMS OF SALT SENSITIVTY IN POPULATIONS AT RISK**

**Renin-angiotensin aldosterone system and primary aldosteronism**

The renin-angiotensin-aldosterone system (RAAS) is the crucial endocrine regulator of BP, maintaining water and sodium homeostasis.20,21 In healthy people, during low salt intake, RAAS is normally activated causing water and sodium retention and rise in BP. In conditions of high salt, RAAS is supressed resulting in sodium and water excretion. In salt sensitivity RAAS tends to be, depending on the salt intake, less responsive or insufficiently suppressed, which is especially observed in black populations. Huan et al.22 suggest that insufficiently suppressed aldosterone is a potential mechanism of salt sensitivity in African-Americans. He et al.23 found a greater fall in BP in black patients compared to Caucasians when changing from high (350 mmol/day for five days) to low (10 mmol/day for five days) dietary sodium intake. Plasma renin activity (PRA), plasma angiotensin II and aldosterone levels increased to a lesser extent in black population. Less responsive RAAS in blacks may be an explanation for greater changes in BP when changing the dietary intake of sodium from high to low. Richardson et al.,15 in their recent review, suggest that high salt intake, salt retention, and/or volume overload lower RAAS activity and cause hypertension in non-Hispanic blacks. Considering older populations, the cut-off values of aldosterone to renin ratios, used to screen for primary aldosteronism, differed in older and younger populations undergone saline infusion tests, with values being higher in the former group, implying an association of salt sensitivity with insufficiently suppressed aldosterone in older populations.24

**Endothelial dysfunction**

The endothelium has a major role in control of vascular tone and in turn, blood flow. It secretes both vasodilator and vasoconstrictor substances, with the main vasodilating molecules being nitric oxide (NO) and Prostacyclin (PGI2).25 Endothelial dysfunction, or more precisely, impaired vasodilation due to reduced endothelial nitric oxide synthase activity and NO production, is related to salt sensitivity of BP.26,27 Increased NO production in the kidney and peripheral vasculature is responsible for the regulation of BP and sodium balance during increased sodium intake.28 With regards to endothelial dysfunction in populations at risk, normotensive salt sensitivity in black populations is associated with an increase in plasma asymmetric dimethyl arginine, an endogenous competitive inhibitor of endothelial nitric oxide synthase, which in turn inhibits vasodilatation.29 A similar response occurs in postmenopausal women. Scuteri et al.30 report higher concentrations of asymmetric dimethyl arginine and lower availability of NO in normotensive postmenopausal salt-sensitive women not receiving oestrogen compared to salt-resistant ones. Even though NO production has been found to decrease in aging salt-sensitive rats,31 Schmidt et al.28 report no similar observations in older salt-sensitive humans. However, one of the limitations of the study may be the small number of participants completing the study diets. Further studies are needed to clarify the possible association of endothelial dysfunction and salt sensitivity in older populations.

**Interplay of oestrogen, renin-angiotensin system and nitric oxide in postmenopausal women**

With oestrogen positively influencing endothelial nitric oxide synthase in the production of NO, and NO being a physiologic antagonist of angiotensin II, the RAAS is considered to be associated with salt sensitivity in women as well.31 It is especially after menopause that changes in renal sodium handling, oxidative stress, and hypertension occur, most likely due to an imbalance between NO and angiotensin II.32 A study conducted on normotensive women in whom menopause was induced surgically, confirmed the protective effect of female sex hormones on salt sensitivity, independent of aging. Results of the study show that prevalence of salt sensitivity doubled four months after the surgery, even though hypertension did not occur. Authors point out that the decrease of oestrogen and the resultant lack of modulation of the RAAS and NO system as the potential mechanisms implicated in postmenopausal salt-sensitive hypertension.33

**Kallikrein-kinin system**

Kallikrein-kinin system is a hormonal system in which the enzyme kallikrein catalyses the production of the vasodilator bradykinin.34 Urinary kallikrein excretion was showed to be lower in salt-sensitive blacks compared to salt-sensitive Caucasians.34 Gainer et al.35 reported enhanced wheal response to exogenous bradykinin under salt replete conditions in African Americans compared to Caucasians, suggesting decreased endogenous bradykinin levels in the former group. African Americans may have impaired function of kallikrein-kinin system compared to Caucasians but further studies are required to provide better insight into kallikrein-kinin system functioning and its association to salt sensitivity in black populations.

**Impaired ion transport**

Kidneys play a major role in dietary salt reabsorption and volume regulation. It is in the thick ascending limb of Henle’s loop where significant amounts of salt, but not water, are reabsorbed, a process mediated by a Na+-K+-2Cl− cotransporter (NKCC2) and sodium pump (Na+-K+-ATPase).36 Aviv et al.,37 in their comprehensive review, suggest enhanced activity of the Na+-K+-2Cl− cotransporter in the thick ascending limb of black populations as the major factor contributing to their high prevalence of salt sensitivity. Related to the sodium pump activity, lower activity has been reported in blacks compared to Caucasians or other races, but with no certain association with salt sensitivity.38,39 However, Wright et al.40 report similar sodium pump activity in postmenopausal hypertensive and normotensive Caucasian and African American women. Nevertheless, authors point to cell type in which the pump activity was measured as one of the potential causes of negative results. Erythrocytes have low sodium pump activity when compared with other cell types and this may have resulted in the inability to demonstrate a racial difference in pump activity.

**Renal hemodynamics**

Impaired renal hemodynamics, more precisely, elevated glomerular filtration rate (GFR) and decreased renal blood flow (RBF) may be associated to salt sensitivity in black populations. In 59 Caucasian and 22 black males with essential hypertension matched for age and BP, while there were no significant differences in RBF, GFR was significantly higher in black patients (P = 0.007) after high salt diet (unrestricted sodium) and it varied directly with the change in MAP. In Caucasian patients there was no significant difference in GFR.41 Results, however, have to be taken into consideration with caution since the authors do not state the exact sodium content of the high salt diet. In 1991, Campese et al.42 investigated renal hemodynamic response to high salt diet in 17 black and nine Caucasian patients with essential hypertension. Patients were placed on a low sodium diet (20 mmol/day) for nine days, followed by a high sodium diet (200 mmol/day) for 14 days. Eleven black and no Caucasian patients were considered as being salt-sensitive when looking at changes in their MAP after high salt diet. During high salt diet, salt-resistant hypertensive patients exhibited an increase in RBF and a decrease in filtration fraction, whereas salt-sensitive, black, hypertensive patients displayed opposite: a decrease in RBF and rise in filtration fraction and intraglomerular pressure.

**Atrial natriuretic peptide**

Atrial natriuretic peptide (ANP) is a peptide secreted by atrial myocytes with natriuretic, diuretic, and hypotensive activity. ANP, among its other effects, influences the change in GFR and inhibits aldosterone secretion from adreno-cortical cells.43 Campese et al.44 compared plasma ANP levels of 13 salt- sensitive and 14 salt-resistant hypertensive blacks with plasma ANP of six salt-sensitive and eight salt-resistant hypertensive whites. Patients underwent low (10 mmol/day) and high (250 mmol/day) sodium dietary protocols in order to determine salt sensitivity. During high salt intake, plasma ANP levels were lower in salt-sensitive blacks compared to their salt-resistant counterparts (P<0.01). It is important to note that high salt intake did not cause any changes in ANP plasma levels in hypertensive whites, suggesting that decreased ANP secretion is a potential cause of salt sensitivity in black populations.

**Sympathetic nervous system activity**

Elevation in extracellular fluid results in increased activity of sympathetic nervous system (SNS), commonly measured by catecholamine levels,45 which can lead to increased vascular smooth muscle contraction, intracellular calcium accumulation and abnormal sodium transport.46 Campese et al.47 suggest that reactive oxygen species (ROS) may increase SNS activity together with increase in BP and that the mechanism may be decreased NO production, disabling this molecule to exert its tonic inhibition of SNS activity. In black patients, a blunted renal dopamine excretion, resulting in decreased natriuresis, may be an explanation of increased BP in response to high salt intake.48 Dustan49 reports a negative correlation of plasma norepinephrine levels and urinary sodium excretion during changes from salt depletion to repletion and vice versa in black hypertensive subjects. In women, oestrogen decreases catecholamine levels with female sex predicting lower urinary and plasma epinephrine and urinary norepinephrine in a study by Saxena et al.50 However, in the same study, no association between plasma or urinary norepinephrine or epinephrine levels was found with hypertension. Change in catecholamine levels between liberal sodium (200– 250 mmol/day) to low sodium diet (10 mmol/day) was also not associated with diagnosis of hypertension. Finally, research is conflicting regarding the SNS activity and its association to salt sensitivity of BP in older populations. Enhanced SNS activity that happens with age may be the cause of salt sensitivity. 51 Conversely, Brown et al.52 and Picirillo et al.53 found no such association. In fact they report diminished SNS activity, measured by norepinephrine levels and heart rate variability, in older people. In addition, the same study shows that SNS activity declines faster in hypertensives and that observed increase in MAP on a high salt diet is not caused by an increase in systemic SNS activity. Considering the discrepancies in these studies, further investigation into this question is needed.

**Genetic basis of salt sensitivity - focus on black populations**

From the studies presented, it is clear that individuals of African origin are at greater risk of salt sensitivity. Indeed, the prevalence of salt sensitivity in this population is higher compared to overall population. It is estimated to be present in 73% of hypertensive and 36% of normotensive blacks.4 Svetkey et al.54 concluded that 26% to 84% of variability in MAP and 26% to 74% in SBP response to sodium loading in black populations can be explained by genetic factors. Since then, a number of candidate genes that may be associated to salt sensitivity have been investigated. Majority of these genes are involved in pathways already described to be possible cause of salt sensitivity. Using the similar approach, Tiffin et al.55 performed computational analysis to determine candidate genes that have significant variability between indigenous South African and white populations. Their search included genes involved in pathways such as RAAS, SNS, ANP, dopaminergic system and ion transport. Of all the genes explored, parathyroid hormone precursor (*PTH*) and type-1angiotensin II receptor (*AGTR1*) were the top ranked candidate genes for salt-sensitive hypertension in indigenous South Africans, warranting further investigation. Furthermore, as previously mentioned, RAAS may be responsible for the control of blood pressure during high sodium intake, especially in black populations. The insertion/deletion polymorphism in the angiotensin-converting enzyme (*ACE*) gene, coding for an enzyme that converts angiotensin I into angiotensin II, may play a role in hypertension. Duru et al.56 report higher frequency of the deletion allele in hypertensive African Americans compared to the ones with normal BP. However, the authors do not mention gene-environment interactions making it difficult to draw any conclusion about salt-sensitive phenotype. Similarly, in Ghanaian population, epistatic interaction of insertion/deletion polymorphism in *ACE* and 65L in the G protein-coupled receptor kinase (*GRK4*) explained 70.5% of variation in BP.57 GRK4 is a serine-threonine kinase that is, among other, responsible for uncoupling of the dopamine receptor from its G protein resulting in its desensitisation. Increased GRK4 activity results in impaired natriuresis and increased BP.58 Blunted dopamine excretion and impaired natriuresis, as mentioned previously, may be the cause of salt sensitivity in black populations. Lohmueller et al.59 investigated genetic variation in *GRK4*, genotyping 13 single nucleotide polymorphisms (SNP) in four different populations: African Americans, Asians, Hispanics and Caucasians. Observed differences in allele and haplotype frequency and structure were most pronounced between African Americans and Asians clearly demonstrating differences in genetic background between populations. It is the A142V polymorphism in *GRK4* gene that may be the factor that predisposed blacks to salt sensitivity compared to whites. The authors of the study report decreased plasma aldosterone and urinary sodium excretion in blacks after infusion of two litres of normal saline (308 mmol of sodium) over two hours.60 In a study conducted one year later, the same authors showed that black patients aged 50 to 75 years exhibit different responsiveness to sodium reduction dietary intervention based on the *GRK4* R65L and A142V polymorphisms. Subjects with TT genotype at both sites did not show a statistically significant decrease in BP after the intervention period.61 Moreover, 65L allele was associated with an increased BP and decreased sodium excretion during stress test in black adolescents, an effect not observed in whites.62

Another potential susceptibility locus for salt sensitivity, related to GRK protein family, is β2-adrenergic receptor (β2-AR). This receptor mediates vasodilatory response to adrenergic agonists.63 Polymorphism G46A of *β2-AR* may be the factor that modifies the BP response to Dietary Approaches to Stop Hypertension (DASH) diet. This dietary pattern is rich in potassium, magnesium, and calcium from fruit and vegetables and low-fat dairy products. It also includes whole grains, poultry, fish and nuts with small amounts of red meat and is low in fat and cholesterol, and has been shown to lower BP.64 In subjects following the high salt (150 mmol sodium/day) and DASH diet, the ones with AA G46A genotype had a greater reduction in SBP after a 30-day dietary intervention, showing a greater responsiveness to a BP lowering effect of DASH. The frequency of the AA genotype was higher in African Americans (27%) than in whites (16%).65

In addition to evident associations between genetic factors and salt sensitivity, dietary salt may cause an increase in BP by interacting with factors responsible for epigenetic modifications. Williams et al.66 investigated the influence of dietary salt on the activity of histone modifying enzyme, lysine specific demethylase 1 (LSD-1). The authors hypothesised that the minor allele of *LSD-1* is associated to decreased enzyme levels and /or loss of function similar to what was previously observed in mice.67 Primary cohort of this study was 63 hypertensive African Americans and the study protocol was replicated in Caucasian and Hispanic populations. After seven days of the low salt (10 mmol sodium/day) and five to seven days of high salt diet (200 mmol sodium/day), two SNPs in *LSD-1*, rs671357 and rs587168, were associated with increase in SBP from low to liberal salt diet in African American cohort. Findings for the SNP rs587168 were replicated in Hispanic cohort but not in Caucasians. Decreased plasma aldosterone and no change in RBF from low- to high salt diet were observed in minor allele carriers. However, authors point out that more research is needed into specific molecular mechanisms that underlie *LSD-1* association to salt sensitivity of BP.

Together with these ethnic differences, sex specific differences have been observed in genetic predisposition to salt sensitivity. In the Han Chinese population, only male minor allele carriers of oestrogen receptor (*ESR1*) SNPs rs9340844, rs9397453, rs9371562, rs9397459, and rs9383951 have shown significant changes in SBP and diastolic blood pressure from low (51 mmol sodium per day) to high-sodium (308 mmol sodium per day) diet.68 Conversely, rs35929607A>G polymorphism of the serine/threonine kinase 39 (*STK39*) gene, a gene involved in sodium reabsorption at the renal tubule, was significantly associated to salt sensitivity only in women in the Salt Reduction to Avoid Hypertension study.69

To summarise, it is problematic to pinpoint the specific physiological mechanism that causes salt sensitivity in populations considered to be at risk. There is an obvious interplay of existing mechanisms found to be related to salt sensitivity in postmenopausal women, older and black populations. A wide range of mechanisms explaining salt sensitivity in the latter compared to other groups does not necessarily mean that some of those mechanisms are not potential causes of salt sensitivity in other populations too. Among others, RAAS and NO are the factors that interact with various other systems described to be associated with salt sensitivity of BP, as shown in Figure 1. In salt-sensitive postmenopausal women, it is the loss of oestrogen that probably mediates the relationship between RAAS and endothelial dysfunction, similarly observed in salt-sensitive black but inconclusive in salt-sensitive older populations. Impaired ion transport, renal hemodynamics and secretion of ANP seem to be more pronounced in black populations compared to white. In addition, increased SNS activity may have a role in development of salt sensitivity, besides black, in older populations and postmenopausal women. More specific research on mentioned mechanisms in these populations is lacking. Finally, it is clear that, especially in blacks, these phenotypic traits are a consequence of gene-environment interactions. Polymorphisms in the *GRK4* gene seem to be particularly associated to salt sensitivity in black populations to date. Nevertheless, considering the complexity of this phenomenon, further research should focus on discovering novel candidate genes for salt sensitivity, gene-gene and gene-environment interactions.

**DIETARY FACTORS AFFECTING SYSTEMS INVOLVED IN SALT SENSITIVITY**

The next two sections will explore micro- and macronutrients affecting systems involved in salt sensitivity. Due to the lack of studies explaining mechanisms of salt sensitivity in older populations, the focus will be on black populations and postmenopausal women. Considering that majority of research is conducted on animals, both human and animal studies will be included with an overview of studies presented in Tables 1and 2.

**Micronutrients**

 **Renin-angiotensin aldosterone system**

 According to studies conducted on both humans and animals to date, potassium and vitamin D exert their beneficial effect on salt-sensitive BP through action on RAAS. Brunner et al.70 show that potassium intake (182.7±10.7 meQ/24 hours potassium chloride) decreases BP and PRA in normotensive and hypertensive subjects. However, lower concentrations of potassium did not result in changes in PRA. 70 Animal studies confirm beneficial effects of adequate potassium intake on salt-sensitive BP. In normotensive salt-sensitive rats, with renal injury caused by high salt intake, potassium depletion (<0.05% potassium for 14 to 21 days) led to an increase in BP. This was accompanied with activation of RAAS, higher PRA and down regulation of angiotensin II receptors.71 In addition to these, a cross sectional study, embedded in the HyperPath cohort study, investigated an association between 25-hydroxyvitamin D (25OHD) and PRA under conditions of low (≤10 mmol/day) and high (≥200 mmol/day) sodium diet in 223 hypertensive, non-diabetic Caucasians. PRA was inversely correlated to 25OHD in low and high sodium balance. In low renin subjects, salt-sensitive BP was associated with significantly higher 25OHD levels when compared to salt-resistant BP (P=0.02) whereas in normal renin hypertensive subjects such an association was not reported, suggesting an important role of renin in vitamin D, RAAS and salt sensitivity association.72 However, Vitamin D may be the micronutrient of special importance to populations of African ancestry since they are considered to have lower plasma 25OHD concentrations compared to Caucasians.73,74 Forman et al.75 investigated normotensive black and white men and women. Participants were placed on high sodium diet (200 mmol/day) and defined as having: optimal (≥30.0 ng/mL), insufficient (15.0 to 29.9 ng/mL), and deficient (<15.0 ng/mL) vitamin D status, expressed as 25OHD plasma levels. The study showed that the insufficient and deficient groups had higher diastolic blood pressure and circulating angiotensin II levels and were more likely to be black.

**Endothelial function and vascular reactivity**

A review by Kanbay et al.,76 reports a positive effect of dietary potassium on endothelial production of transforming growth factor (TGF-β) during high saltintakes. TGF-β is a growth factor produced in the endothelium and other tissues, and is considered to have a role in BP regulation. Increased production of this factor leads to vasoconstriction and an increase in BP.77 Moreover, NO produced by the endothelium may be a mediator in TGF-β synthesis, especially during a high salt diet, exerting its protective effects on salt-sensitive BP.78 In a normotensive adult Chinese rural population, potassium supplementation (4.5 g/day, KCl) reduced BP, asymmetric dimethyl arginine levels and increased NO production in salt-sensitive but not salt-resistant subjects.79 Liu et al.80 report a beneficial effect of potassium supplementation on vascular function in a Chinese population. In their study population of normotensive and mildly hypertensive salt-sensitive men and women, short term BP variation and vascular function expressed as ambulatory arterial stiffness index improved after potassium supplementation. A high salt intervention (307.7 mmol sodium/day) signiﬁcantly increased BP, ambulatory arterial stiffness index, symmetric ambulatory arterial stiffness index (P<0.001) and vasoconstrictor peptide, endothelin levels (P<0.05). These effects were more pronounced in the salt-sensitive population. Sixty mmol of potassium chloride daily during a week on a high salt diet (18g of salt or 307.7 mmol sodium/day) resulted in improved SBP and endothelin levels (P<0.001). In contrast, Wang et al.81 investigated the effect of potassium supplementation on pulse wave velocity (a commonly used measure of arterial stiffness) in a salt-sensitive and salt-resistant Chinese population. Even though potassium supplementation resulted in decreased BP in salt-sensitive subjects on a high salt diet (P<0.05), no statistical differences in pulse wave velocity were observed on potassium supplementation, when compared to the high salt diet only, and furthermore, no correlation of pulse wave velocity and urinary sodium or potassium excretion were found.

In animal studies,82 dietary potassium attenuated salt induced acceleration of vascular injury. Dahl salt-sensitive (Dahl S) and Dahl salt-resistant rats were fed either a normal salt diet (0.3% NaCl), a high salt diet (8% NaCl) or a high salt + high potassium (8% NaCl + 8% KCl) diet for five weeks. Salt loading resulted in increased BP, accelerated neointima proliferation, increased superoxide production and nicotinamide adenine dinucleotide phosphate induced superoxide production in arteries of salt-sensitive rats. Potassium supplementation slightly decreased BP in salt-sensitive rats but was more efficient in counteracting salt induced acceleration of neointima proliferation in the same group. Potassium supplemented salt-sensitive animals had lower nicotinamide adenine dinucleotide phosphate oxidase activity which may result in improved vasculature function in salt-sensitives. In addition to potassium**,** antioxidant vitamins may have a protective effect on salt-sensitive changes in BP due to their action on endothelial function, more precisely NO production and vascular reactivity. Vitamin C was found to have a protective effect on salt-sensitive BP increase in male Sprague Dawley rats. Rats were fed: a standard diet, a high sodium (8% NaCl) diet, a standard diet plus vitamin C (100 mg/kg/day), or a high sodium diet plus vitamin C for six weeks. As expected, the high salt diet resulted in increased BP. Vitamin C supplementation caused an opposite effect. It was proposed that vitamin C exerts its beneficial effects through increased NO production and reduces vascular reactivity to norepinephrine.83 When supplemented with 34mg/kg feed/day of vitamin E, Dahl S rats exhibited a decrease in BP. An increase in tissue aldehyde conjugates resulting in increased cytosolic calcium levels, vascular smooth muscle hyperplasia in kidneys, and increased BP during a normal salt (0.7% NaCl) diet was attenuated with vitamin E supplementation.84 Similarly, when supplemented with alpha tocopherol (1000U/kg of feed) Dahl S rats exhibited an increase in cyclic guanosine monophosphate levels,85 as a consequence of increased NO bioavailabilty, reduced due to oxidative stress.

**Kallikrein-kinin system**

Potassium supplementation (2% KCl in water) was associated with increased tissue kallikrein synthesis and excretion as well as downregulation of renal TGF-β in Sprague Dawley female rats. The mice were fed normal salt diet (0.4% NaCl) and then, to induce salt sensitivity, a high salt diet (4% NaCl) during the final week of a four week experiment.86 Imparied kallikrein-kinin system functioning, more precisely, lower urinary kallikrein excretion, leads to a conclusion that, once again, potassium is the micronutrient of high importance in this population. However, human studies are needed to support this assumption.

**Ion transport and natriuresis**

Dietary potassium deficiency may activateNa-Cl cotransporter (NCC) in the conditions of high salt intakecausing large amounts of salt to be reabsorbed in the kidneys and consequently a rise in BP.87 As for the animal studies, Jung et al.88 investigated the effect of uninephrectomy, the surgical removal of one kidney, and a high salt diet on the development of hypertension and ion transport in Sprague Dawley rats. Rats were uninephrectomized and placed on a normal salt diet (0.3% NaCl) for four weeks. After the first four weeks of experiment animals were placed either on a high salt diet (8% NaCl) or a high salt diet supplemented with potassium (8% NaCl + 1% KCl given as a substitute for drinking water). Surgery, as expected, resulted in the high salt diet causing a significant rise in SBP, but with less of an increase in the group receiving potassium supplementation (P<0.04). Similar to the findings of the previous study, the protein abundances of type 3 Na/H exchanger and NCC in the potassium supplementation group were decreased and the authors proposed a natriuretic effect of potassium, associated with a decreased expression of NCC, as a mechanism responsible for these favourable effects.88

**Renal hemodynamics**

To our knowledge, potassium and calcium are the micronutrients with the most pronounced effects on renal hemodynamics. Schmidlin et al.89 investigated the effects of potassium supplementation (170 mmol/day (KHCO3)) in 10 salt-sensitive and six salt-resistant, normotensive or mildly hypertensive black patients. They found that dietary potassium may have a protective effect on renal hemodynamics, more precisely GFR and filtration fraction in the observed salt-sensitive population. Calcium, on the other hand, may act beneficial on renal hemodynamics by affecting systemic and renal vasculature. In a study by Rich et al.,90 beneficial effects of calcium on BP were observed in an adult Caucasian population. Participants were receiving calcium supplementation during low and high salt loading periods. Compared to low salt BP, high salt diet increased the BP. The increase was lower in subjects receiving high salt diet with calcium supplementation (high calcium diet) compared to high salt and low calcium diet. RBF, expressed as P-aminohippurate clearance increased to a higher extent on high salt/high calcium diet compared to high salt/low calcium (P<0.05). Data from animal studies suggest similar protective effects of calcium supplementation. Salt-sensitive spontaneously hypertensive rats (SHR) fed a calcium supplemented diet (4%) exhibited lower BP increase after a high salt diet (8%) over a four week period compared to a control group not receiving calcium supplementation. The high salt diet alone resulted in elevated MAP and increased renal vascular resistance. Calcium supplementation counteracted these changes. The authors proposed that the calcium had a beneficial effect on renal vasculature and normalisation of renal haemodynamics.91

From the studies discussed and presented in Table 1., potassium stands out as the micronutrient affecting number of systems involved in development of salt sensitivity. It can be recommended as the micronutrient of utmost importance in black populations considering its effect on ion transport. Furthermore, it has been shown that potassium may have a positive effect on kallikrein synthesis and GFR, mechanisms also impaired in this population. Lower vitamin D levels observed in populations of African ancestry compared to Caucasians, and its possible effect on RAAS system in conditions of high sodium, makes blacks, once again, a population that should be especially advised on increasing their intakes of this fat-soluble vitamin. Postmenopausal women could benefit from increased potassium and antioxidant vitamin rich foods. It is due to their effect on NO production, a substance often not synthesised in enough quantities in this population.

**Macronutrients, their interactions and dietary patterns**

**Renin-angiotensin aldosterone system**

As mentioned previously, DASH dietary pattern has been shown to have a beneficial effect on BP. Results of clinical trials confirm this in participants on three different sodium levels “higher” (approximately 143 mmol/day, reflecting typical US consumption), “intermediate” (106 mmol/day, reflecting the upper limit of current US recommendations), and “lower” (65 mmol/day, reflecting a level that could produce an additional lowering of BP).64,92 DASH was found to decrease sensitivity to salt in both normotensive and hypertensive populations. It has been found to interact with RAAS, increasing aldosterone levels and PRA in African American and white populations following the high salt (150 mmol sodium/day) diet.65 Opposite to micronutrient and DASH effects, alcohol exerts its unfavourable effects on salt-sensitive BP by affecting RAAS. Di Gennaro et al.93 examined the link between chronic alcohol consumption and salt sensitivity. The study participants were 30 detoxified alcoholics (being detoxified for six to 12 months) and 30 teetotaller controls. Participants underwent a dietary intervention study receiving a 55 mmol sodium/day diet for seven days, followed by a 260 mmol sodium diet for an additional seven days and were classified as salt-sensitive or salt-resistant. Salt sensitivity was determined based on six different criteria using different cut-off points for the changes in MAP. Long-term detoxified chronic alcoholics exhibited more significant changes in BP in response to dietary salt intake. Moreover, salt sensitivity was more prevalent in alcoholics than in controls, regardless of BP levels. The RAAS response, more precisely PRA response to different sodium intakes, was blunted in the detoxified alcoholics group.

**Endothelial function – Nitric oxide production**

High protein intake may have beneficial effects on salt-sensitive BP and arginine is, most likely, the component with these protective effects.94 This semi-essential amino acid found in soy, meat, fish, lentils, beans, whole grains and nuts, but also formed endogenously in kidney and liver is a substrate for NO production.95 Vasdev and Gill,94 in their comprehensive review, report several studies that demonstrate the BP-lowering properties of arginine (either as intraperitoneal, intravenous, or intramedullary infusions or oral supplementation in drinking water) in Dahl S rats on high salt diets (8% Na).96-97 In Dahl S rats, arginine supplementation increased urinary cyclic guanosine monophosphate–adenosine monophosphate levels and NO production,96 normalized renal hemodynamics98 and improved endothelium dependent vasodilation by decreasing endothelium contracting factor levels.99 Arginine supplementation led to a reduction in nicotinamide adenine dinucleotide phosphate -oxidase activity, which rapidly eliminates NO.100 One study conducted on humans showed the similar beneficial effect. Campese et al.101 conducted a study on 21 hypertensive and five normotensive (salt-sensitive and salt-resistant) African Americans. After a high salt diet, BP decrease was highest in salt-sensitive subjects on arginine supplementation (500 mg/kg for 30 min). Effective renal plasma flow response to arginine was improved in both salt-sensitive and salt-resistant group, however, it was more pronounced in salt-resistant subjects. In contrary**,** diet high in fat and sucrose caused an opposite effect on NO production, as reported in the animal study. Roberts et al.102 investigated female Fisher rats on a high fat/sucrose or a low fat/complex carbohydrates diet over a period of two years. The high fat/sucrose diet was high in saturated and monounsaturated fat (primarily from lard plus a small amount of corn oil) and high in reﬁned sugar (sucrose) whereas the low fat/complex carbohydrates diet was low in saturated fat and contained mostly complex carbohydrate (starch). Rats on the high fat/sucrose diet exhibited an increase in BP whereas no change in BP was observed in rats on the low fat and complex carbohydrates diet. After one week of high salt diet (4% NaCl), the pressor response to salt was significantly higher in the former and remained unchanged in the latter group. Renal nitric oxide synthase activity and NO production were lower in the rats on the high fat/sucrose diet. 100

**Ion transport and natriuresis**

Besides its protective effects on RAAS, DASH dietary pattern can be beneficial in the cases of impaired ion transport and natriuresis. Akita et al.19 observed an increased slope in the pressure-natriuresis curve, without shifting the curve to the right, in 215 African Americans and 157 whites on DASH, suggesting natriuretic properties of this dietary pattern. The slope was shallower in hypertensives than in normotensives, in African Americans than in other races, as well as in older (over 45 years) than in younger participants, indicating that BP was more sodium sensitive in the former subgroups than in their latter counterparts. Interestingly, this was not observed in the female population. Potassium and calcium may be the components that are responsible for this effect, but other nutrients are probably contributing, making the BP lowering effect of DASH more pronounced. Contrary to the beneficial effects of DASH, fat and fructose, have been shown to interfere with ion transport in kidneys. Angiotensin II has an effect on ion transport by influencing sodium/hydrogen exchanger and 5' adenosine monophosphate-activated protein kinase activity. Fructose fed Sprague-Dawley rats did not show an increase in BP while being fed only with fructose (20%) for seven days. Adding salt (8% NaCl) to their diet caused a statistically significant increase in SBP (P<0.05). The authors found that acute fructose augments the ability of angiotensin II to stimulate luminal sodium/hydrogen exchanger activity in the proximal tubule causing sodium reabsorption and rise in BP.103 High fat diet fed salt-sensitive rats developed obesity related salt-sensitive hypertension after 12 weeks accompanied with an increase in SBP. This rise in BP was associated with sodium retention caused by an increase in AII contents and inactivation of 5' adenosine monophosphate-activated protein kinase in the kidney,104 showing an association between obesity related changes in metabolic parameters and rise in BP in salt- sensitive population.

 **Sympathetic nervous system activity**

As previously discussed, even though evidence is scarce, SNS activity may be associated with salt sensitivity in populations at particular risk of salt sensitivity. Fang et al.105 investigated ovariectomized female SHR, a breed that develops salt-sensitive hypertension when oestrogen depleted, and suggested beneficial effect of dietary phytoestrogens commonly found in soy on BP and SNS activity in these animals. On the other hand, high sucrose and fat dietary intake have been shown to increase SNS activity. Sprague Dawley rats exhibit an increase in BP after ingesting sucrose-sodium diet.106,107These rats exhibit a significant increase (P<0.001) in SBP after four weeks of consuming high sodium (4% NaCl), high sucrose diet (receiving sucrose in their drinking water; 7% by weight) compared to their counterparts fed either: a low sodium (0.45% NaCl), no sucrose; a low sodium, high sucrose; or a high sodium, no sucrose diet. Even though high sodium diet did not cause a statistically significant increase in cateholamine levels, the authors suggest that activation of the SNS is one of the possible mechanisms of the increase in BP. They state, however, that hypertension is developed only when an adequate amount of salt is consumed together with sucrose.107 Nagae et al.108 report somewhat similar in rats on the high fat diet. Ahigh fat intake during eight weeks was associated with increased SBP in high salt-fed Dahl S rats (8% NaCl). Although the rats exhibited an increase in BP during both high (45% fat) and low fat (10% fat) diets, the sodium pressor effect was more pronounced in high fat-fed rats. The latter group also accumulated more visceral fat and gained more weight. Finally, catecholamine levels were increased in the early phase of fat loading, suggesting that it is insulin resistance developed due to visceral fat accumulation and resultant increase in SNS activity that caused a rise in BP.

In summary, less responsive RAAS, a trait of salt sensitivity in blacks, suggests it is the population to be particularly advised on reducing alcohol intake. On the other hand, because of this trait and the impaired natriuretic mechanisms of blacks, it can be assumed that this population would especially benefit from dietary patterns similar to DASH. It is due to its interaction with RAAS and increased natriuresis observed in African Americans. Furthermore, black populations should be advised on restricting their saturated fat and sucrose intake, as a result of their impact on NO bioavailability in conditions of high salt intake. In order to increase bioavailability of this vasodilating substance, dietary intake of l-arginine rich foods should be increased. As previously mentioned, in salt-sensitive postmenopausal women, it is the loss of oestrogen that probably mediates the relationship between RAAS and endothelial dysfunction. Thus, l-arginine rich food and dietary patterns similar to DASH should be encouraged while intake of saturated fat and sucrose should be reduced. With regards to SNS activity, at this time it is unclear whether regular consumption of soy, as the main source of dietary phytoestrogen, would benefit this population. Even though oestrogen has been shown to reduce the catecholamine levels, the change in catecholamine levels between low- and high salt diet was not associated with diagnosis of hypertension in postmenopausal women. An overview of macronutrients, dietary patterns and lifestyle factors affecting different mechanisms involved in development of salt sensitivity is presented in Table 2.

**MAGNESIUM, MACRONUTRIENT CONTENT OF THE DIET AND PHYSICAL ACTIVITY ALSO CONTRIBUTE TO SALT SENITITIVY**

In addition to factors influencing systems involved in salt sensitivity of BP already presented, certain dietary and lifestyle factors provide a potential for future research as mechanisms of their actions need to be further explored.

Together with changes in intra- and extra-cellular sodium and calcium, changes in magnesium levels are associated with high salt intake and these changes are more apparent in salt-sensitive populations.109,110 In African American salt-sensitive subjects on a high salt diet, calcium to magnesium ratio was higher compared to salt-resistant or salt-sensitive Caucasian individuals suggesting an association between magnesium and salt sensitivity in this population.40 An association between magnesium and salt sensitivity has been found in animal studies as well. Abnormal magnesium metabolism has been observed in the model of genetically predisposed salt-sensitive rats. Magnesium concentrations in erythrocyte ghosts, aortas, and mesenteric arteries of female salt-sensitive (SS/JR) and salt-resistant (SR/JR) Dahl-derived rats were lower compared to a Sprague Dawley control group. Both groups were fed normal rat chow and either tap water or 0.9% NaCl. High salt did not have an effect on magnesium levels in the control group whereas salt-sensitive rats developed hypertension. The authors suggest a possible inheritable metabolic defect that disables the magnesium binding to plasma membrane of cells which, in turn, may be associated with hypertension development in these animals. However, they also state that this defect is probably not the sole cause of salt-sensitive hypertension but one of the contributing factors.111 Furthermore, emphasizing the importance of the macronutrient content of the diet, Mattson et al.112 investigated the development of salt-sensitive hypertension in inbred Dahl rats (Dahl SS/Mcw). A significant reduction in MAP was observed when substituting the casein with wheat gluten on either a high (4% NaCl) or low (0.4% NaCl) intake compared with rats on the AIN-76A diet containing 50% sucrose, 20% casein, 15% corn starch, 5% cellulose and 5% corn oil. Furthermore, the rats fed the whole-grain diet had significantly lower MAP compared to the rats fed the AIN-76A diet. Regardless of the sodium intake, a substitution of corn oil with soybean oil resulted in the highest increase in MAP. Finally, together with alcohol consumption, another potential lifestyle correlate of salt sensitivity is participation in physical activity. To our knowledge, only one study reports this association. A large dietary feeding study was conducted among 1,906 individuals who were 16 years of age or older and living in rural northern China. Participants underwent a seven day low sodium intervention (51.3 mmol sodium/day) followed by a seven day high sodium intervention (307.8 mmol sodium/day) to determine salt sensitivity. Usual physical activity during the past 12 months was assessed at baseline using a standard questionnaire. The study found physical activity level to be a strong predictor of the SBP response to dietary sodium. These observations persisted when taking into consideration possible confounders (age, sex, body mass index, educational level, cigarette smoking, alcohol consumption, and baseline urinary excretion of sodium and potassium).113 Given that only one study has reported this association, it is hard to draw a conclusion whether salt-sensitive patients would particularly benefit from regular physical activity.

**CONCLUSION**

The purpose of this review was to identify the possible mechanisms of salt sensitivity in populations that are at particular risk, together with dietary and lifestyle factors that may act protective or harmful by affecting these systems. Based on the research conducted to date it is suggested that blacks, postmenopausal women and older populations are the populations that tend to be more salt-sensitive and thus at greater risk of developing hypertension and CVD. Due to small number of studies investigating potential mechanisms of salt sensitivity in populations aged 65+ years, the focus of this review were mainly black populations and postmenopausal women. While some mechanisms underlying salt sensitivity in these populations are thoroughly investigated, other areas require further investigation such as gene-environment interactions, SNS and its role in development of salt sensitivity or the functioning of kallikrein-kinin system in blacks. A wide range of mechanisms explaining salt sensitivity in the latter group does not necessarily mean that some of those mechanisms are not potential causes of salt sensitivity in postmenopausal women too. Even though studies on dietary factors influencing mechanisms of salt sensitivity presented in this review have not all been conducted on the populations of our particular interest, certain conclusions can be drawn. An increase in BP observed in these two demographic groups in conditions of high salt intake, can be blunted depending on the dietary intake. Higher intakes of potassium, calcium, vitamin D, antioxidant vitamins, proteins rich in amino acid l-arginine, and adherence to dietary patterns similar to DASH can be especially beneficial. It is due to their action on RAAS, endothelial function, renal hemodynamics and ion transport. In contrast, diets similar to typical Western diet, rich in saturated fats, sucrose and fructose together with excessive alcohol consumption, affecting mentioned mechanisms, may exacerbate salt-sensitive changes in BP in these populations leading to faster onset of hypertension and/or CVD. Future research into diet and salt sensitivity should focus on investigating the complex composition of diet and dietary patterns that affect these mechanisms, as it has been shown that nutrient-nutrient interactions have an important role in salt sensitivity. Considering that the majority of studies on this particular topic have been conducted in animal models, further human studies are required to be able to give more specific recommendations. These studies should include primarily populations described at being at higher risk. Finally, future research into other lifestyle factors and salt sensitivity is recommended as a part of the more comprehensive understanding of this phenomenon.

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**FIGURES AND TABLES**



*Abbreviations*: ANP, atrial natriuretic peptide; BP, blood pressure; GFR, glomerular filtration rate; NKCC2, sodium-potassium-chloride cotransporter; NO, nitric oxide: RAAS, renin-angiotensin aldosterone system; SNS, sympathetic nervous system.

Figure 1 **Schematic overview of the most prominent systems associated with salt sensitivity in populations at risk.** In salt-sensitive black individuals RAAS is insufficiently suppressed during a high dietary salt intake resulting in higher aldosterone levels, which in turn causes water and sodium retention and an increase in BP. Decreased ANP secretion, during high dietary salt intakes, observed in the same population may be associated with higher aldosterone levels as well as with higher GFR. In addition, decreased kallikrein synthesis results in decreased vasodilator bradykinin levels and salt-sensitive increase in BP in African Americans. Finally, in this population, an increased NKCC2 activity was observed, resulting in sodium retention and increase in BP. Vasodilator NO is an angiotensin II antagonist, with oestrogen considered as the mediating factor of RAAS and NO association in postmenopausal salt-sensitive women. Due to the higher ADMA levels, an endogenous inhibitor of nitric oxide synthase, in salt-sensitive blacks and postmenopausal women, NO bioavailability in conditions of high sodium is lower, resulting in increased BP. Dashed arrows represent potential pathways contributing to hypertension that warrant further investigation in salt-sensitive populations described in this review.

Table 1 **Overview of evidence associating micronutrients with salt sensitivity in human and animal studies.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Nutrient** | **Effect**  | **Study population/animals** | **Mechanism**  | **Reference** |
| **Human studies** |  |  |  |  |
| Potassium | Protective | Normotensive and hypertensive adults | Action on RAAS  | Brunner et al. (1970)70 |
| Normotensive Chinese adults | Improved endothelial function  | Fang et al. (2006)79 |
| Normotensive to mild hypertensive Chinese adults | Improved vascular reactivity  | Liu et al. (2013)80 |
| Normotensive to mild hypertensive black adults | Normalised renal hemodynamics  | Schmidlin et al. (1999)89 |
| Calcium | Protective | Hypertensive Caucasian adults | Normalised renal hemodynamics | Rich et al. (1991)90 |
| Vitamin D  | Protective | Hypertensive Caucasian adults | Action on RAAS  | Vaidya et al. (2011)72 |
| **Animal studies** |  |  |  |  |
| Potassium | Protective | Sprague Dawley rats | Action on RAAS  | Ray et al. (2001)71 |
| Sprague Dawley rats | Improved tissue kallikrein synthesis | Ardiles et al. (2013)86 |
| Sprague Dawley rats | Improved ion transport | Jung et al. (2011)88 |
| Dahl S and Dahl R rats | Improved vascular reactivity | Kido et al. (2008)82 |
| Calcium | Protective | SHR rats | Normalised renal hemodynamics  | Ono et al. (1994)91 |
| Vitamin C | Protective | Sprague Dawley rats | Improved endothelial function and vascular reactivity  | Ettarh et al. (2002)83 |
| Vitamin E | Protective | Dahl S and Dahl R rats | Improved endothelial function | Forde et al. (2003)85 |
| Dahl S rats | Improved vascular reactivity | Vasdev et al. (2005)84 |

*Abbreviations:* Dahl S, Dahl salt-sensitive; Dahl R, Dahl salt-resistant; RAAS, renin-angiotensin aldosterone system; SHR, spontaneously hypertensive rats

Table 2 **Overview of evidence associating macronutrients/dietary patterns and alcohol with salt sensitivity in human and animal studies.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Nutrient/Dietary pattern** | **Effect**  | **Study population/animals** | **Mechanism**  | **Reference** |
| **Human studies** |  |  |  |  |
| L-arginine | Protective | Hypertensive and normotensive African American adults | Improved renal circulation in both salt-sensitive and salt-resistant group (effect more pronounced in salt-resistant group)  | Campese et al. (1997)101 |
| DASH diet | Protective | Normotensive and hypertensive African American and Caucasian adults  | Increased natriuresis | Akita et al. (2003)19 |
| Normotensive and hypertensive African American and Caucasian adults | Action on RAAS  | Sun et al. (2010)65 |
| Alcohol | Harmful | Detoxified adult alcoholics | Action on RAAS | Di Gennaro et al. (2000)93 |
| Fructose | Harmful | Sprague Dawley rats | Impaired ion transport | Cabral et al. (2014)103 |
| Sucrose | Harmful | Sprague Dawley rats | Increased SNS activity | Johnson et al. (1993)107 |
| Fat | Harmful | Dahl S rats | Increased insulin resistance and SNS activity  | Nagae et al. (2009)108 |
| Dahl S rats | Impaired ion transport | Deji et al. (2012)104 |
| **Animal studies** |  |  |  |  |
| L-Arginine | Protective | Dahl/Rapp (SS/Jr) and (SR/Jr) rats | Improved endothelial function  | Chen and Saunders (1991)96 |
| Sprague Dawley and Dahl S rats | Improved renal circulation | Rajapakse and Mattson (2011)97 |
| Dahl S and Dahl R rats | Improved endothelial function | Zhou et al. (2001)99 |
| Dahl S rats | Improved endothelial function  | Fuji et al. (2003)100 |
| Dahl-Iwai S rats and Dahl-Iwai R rats | Normalised renal hemodynamics | Tomohiro et al. (1997)98 |
| High fat/sucrose | Harmful | Fisher rats | Impaired endothelial function  | Roberts et al. (2003)102 |
| Soy (dietary phytoestrogens) | Protective | Ovariectomized SHR female rats | Decreased SNS activity | Fang et al. (2001)105 |

*Abbreviations:* Dahl S/SS, Dahl salt-sensitive; Dahl R/SR, Dahl salt-resistant; DASH, dietary approaches to stop hypertension; RAAS, renin-angiotensin aldosterone system; SHR, spontaneously hypertensive rats; SNS, sympathetic nervous system.