HHS Public Access

Author manuscript

Curr Hypertens Rep. Author manuscript; available in PMC 2020 June 23.

Published in final edited form as:

Curr Hypertens Rep. ; 21(6): 42. doi:10.1007/s11906-019-0948-5.

The Influence of Dietary Salt Beyond Blood Pressure

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Abstract

Excess sodium from dietary salt (NaCl) is linked to elevations in blood pressure (BP). However, salt sensitivity of BP varies widely between individuals and there are data suggesting that salt adversely affects target organs, irrespective of BP. For example, high dietary salt has been shown to adversely affect the vasculature, heart, kidneys, skin, brain, and bone. Common mediators of the target organ dysfunction include heightened inflammation and oxidative stress. These physiological alterations may contribute to disease development over time. Despite the adverse effects of salt on BP and several organ systems, there is controversy surrounding lower salt intakes and cardiovascular outcomes. Our goal here is to review the physiology contributing to BP-independent effects of salt and address the controversy around lower salt intakes and cardiovascular outcomes. We will also address the importance of background diet in modulating the effects of dietary salt.

Keywords

dietary salt; dietary sodium; blood pressure; cardiovascular health; organ damage; vascular physiology

Introduction

Americans' predilection for dietary salt has resulted in mean daily sodium (Na^+) intake of ~3500 mg/d despite multiple organizations recommending ≤ 2300 mg/d (1•, 2). Recommendations to reduce dietary Na^+ are primarily based on studies demonstrating a positive association between Na^+ intake and systolic blood pressure (BP) (3, 4). Clinical trials have demonstrated BP-lowering effects down to a Na^+ intake of 1500 mg/d (5). Recent meta-analyses and systematic reviews of randomized clinical trials (RCTs) have found significant reductions in systolic BP with dietary Na^+ restriction, particularly in individuals with hypertension (6–8). In addition, pre-clinical and clinical studies have demonstrated that high Na^+ adversely affects multiple target organs independent of BP. Thus, guidelines to avoid high dietary Na^+ are supported by a wide range of physiological and clinical studies. However, there is some controversy regarding population-wide efforts to reduce Na^+ intake. While there is agreement that high Na^+ intake (> 5000mg/d) is harmful, several cohort studies have demonstrated a paradoxical *increase* in cardiovascular (CV) events with *lower* Na^+ intake (9–12). This review article will 1) highlight recent data suggesting that high

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dietary Na^+ can cause target organ damage independent of BP (summarized in central figure); 2) review the epidemiological outcome studies that *support* Na^+ reduction efforts; 3) review the cohort studies that suggest Na^+ reduction efforts may have potential negative effects on CV outcomes; and 4) highlight eating patterns that may modulate the relation between salt and CV health.

Salt and target organ effects: BP independent effects of salt

Arteries

Rodent studies demonstrate impaired endothelial function during Na^+ loading, without alterations in BP (13–15). Our lab and others have found that high dietary salt adversely affects both large (16–22) and small (23, 24) artery function in humans. Both salt resistant and salt sensitive participants demonstrate impaired endothelial function following high salt diets (16) and females seem to be modestly protected compared to males (17, 22). We recently demonstrated that a high salt diet increased arterial stiffness in healthy middle-aged adults but the relation was mediated by changes in mean BP (20). The high salt diet also elicited greater forward and reflected wave amplitudes (20). A recent meta-analysis of human trials also suggests that Na^+ reduction reduces arterial stiffness (25). While most of the studies discussed herein were short-term (> five days) controlled feeding studies, there are acute feeding studies in humans demonstrating a single high salt meal impairs endothelial function and increases arterial stiffness (26, 27).

Multiple rodent (13–15, 28) and human studies (23, 24) demonstrate that the negative effects of high Na^+ on the vasculature are mediated by reactive oxygen species (predominantly superoxide, O_2^-). High dietary salt results in an increase in O_2^- which decreases nitric oxide (NO) bioavailability by scavenging NO to form the more stable peroxynitrate radical ($ONOO^-$), or by $O_2^-/ONOO^-$ uncoupling NO synthase (23, 29, 30). Thus, high dietary Na^+ impairs endothelial function through reduced NO bioavailability (31, 32). In addition to increasing oxidative stress, high Na^+ may decrease anti-oxidant defense mechanisms. Specifically, rodent models have demonstrated high Na^+ reduces expression of copper/zinc-dependent superoxide dismutase (SOD), which catalyzes the reduction of O_2^- to hydrogen peroxide (15, 33). This can be prevented by administering sub-pressor doses of angiotensin II (33) (which is suppressed during high Na^+ diets) and regular exercise (15)••. There are also cellular studies demonstrating hypernatremia results in degradation of the endothelial glycocalyx, which may also contribute to impaired endothelial responsiveness to shear stress and vasodilatory agonists (34).

Dietary salt also increases circulating endothelin-1 (26) and arginine vasopressin (35–37), two potent vasoconstrictors. A pro-constrictive vasculature is thought to contribute to augmented sympathetic vascular transduction (i.e., vasoconstrictor responses to bursts of sympathetic nerve activity) (38) and we recently demonstrated dietary Na^+ restriction (down to 1000 mg/d) reduced sympathetic vascular transduction (39)••. Taken together, several human studies have demonstrated that dietary salt contributes to vascular dysfunction and pre-clinical studies have identified several potential pathways through which this dysfunction may occur.

Kidneys

Salt-sensitive hypertension is associated with impaired fluid excretion which contributes to transient increases cardiac output (40)•. With high salt intake, total peripheral vascular resistance may initially decrease due to reflex/hormonal mechanisms that cause vasodilation (e.g., the baroreflex or suppression of angiotensin II) in response to salt-induced volume loading, but normally returns to basal values within several days (40). However, renal dysfunction, characterized by impaired pressure natriuresis has been demonstrated in experimental models of salt-sensitive BP and human salt-sensitive hypertension (40). Normally, high levels of dietary Na^+ suppress the renin-angiotensin-aldosterone system (RAAS) (16, 17, 41), contributing to reduced Na^+ reabsorption. The epithelial Na^+ channel (ENaC), an effector of RAAS expressed in the distal nephron of the kidney, plays a critical role in regulation of Na^+ reabsorption. ENaC has been shown to contribute to increases in serum Na^+ and/or plasma volume expansion in the setting of salt-sensitive hypertension (42). Generally, Na^+-driven reabsorption is diminished in response to salt loads; however, in salt-sensitive rodent models, ENaC protein abundance and activity are paradoxically increased, potentially as a result of high-salt induced renal damage (43, 44). As discussed in our prior review, salt sensitivity of BP increases with age (45), and aging-related changes in renal Na^+ handling may contribute to this increased salt sensitivity (46).

Heart

Salt sensitive rodent models demonstrate heart failure subsequent to pathological left ventricle (LV) remodeling and the development of hypertension with high Na^+ (47). In humans, LV mass is also associated with hypertension (48, 49). Independent of BP, high dietary Na^+ may increase LV wall thickness and mass (50). In a longitudinal study of patients who underwent prospective treatment of essential hypertension over three years, LV mass progressively increased across Na^+ tertiles only in patients with high plasma aldosterone concentrations. This relation demonstrates a potential interaction between high Na^+ consumption and lack of appropriate aldosterone suppression on LV mass (51). Recent data demonstrate that individuals with masked hypertension have higher Na^+ excretion and LV mass (48). Separately, LV mass was independently associated with Na^+ excretion (48). Another recent study that entailed a prospective analysis of diastolic function and LV mass index in participants with elevated BP found that the dietary Na^+:potassium (K^+) ratio was associated with higher LV mass (52). Estimated Na^+ consumption was also positively associated with atrial filling fraction (52). However, Na^+ and K^+ intake were ascertained using a block food frequency questionnaire whereas the other original studies discussed in this section used 24-hour urinary Na^+ excretion (24hU-Na^+), thus the findings from this final study must be interpreted with caution (53).

Skin and inflammation

Two recent excellent reviews have highlighted several studies demonstrating Na^+ loading results in non-osmotic Na^+ accumulation in skin and muscle without commensurate increases in skin water content (54, 55)••. Immune cells including macrophages function as local on-site sensors of interstitial electrolyte concentration and activate tonicity-responsive enhancer binding protein, which increases the expression of vascular endothelial growth

factor C (VEGF-C) gene via autocrine signaling (54, 55). VEGF-C facilitates lymphangiogenesis enabling drainage of water and electrolyte from the skin into the systemic circulation for eventual removal via the kidneys (55). In rodents, macrophage or VEGF-C antagonism or genetic deletion results in augmented interstitial hypertonic volume retention and elevated BP (56, 57). Another recent study demonstrated that high salt increased whole body Na^+ without increases in body water (58). Taken together, these findings would suggest that non-osmotic Na^+ deposition plays a functional role in whole body Na^+ homeostasis and BP regulation. However, it has also been shown that T cells exposed to local high Na^+ tissue conditions polarize into highly pro-inflammatory T_H17 phenotype cells that produce inflammatory cytokines and worsen experimental autoimmune disease and may contribute to hypertension (59, 60).

In agreement, recent human studies have demonstrated skin Na^+ is a marker of aging and hypertension (61). Excess skin Na^+ deposition has also been observed in patients with type 2 diabetes (62), hyperlipidemia (63), and is associated with cardiac hypertrophy in chronic kidney disease (64). Further, a recent study randomized healthy participants to consume low and high salt diets in a crossover design (65)••. Skin Na^+:K^+ increased on the high salt diet in male, but not female participants. Female participants experienced an increase in BP on the high salt, but this may have been confounded by their lower basal BP. Further, in male participants skin Na^+:K^+ correlated with BP. There is some thought that increased skin Na^+ occurs after sufficient vascular damage resulting in a 'leak' into the surrounding tissue (54). Using this line of reasoning, the finding that only males experienced an increase in skin Na^+ with high salt is supported by prior studies demonstrating that high Na^+ damages the endothelial glycocalyx (34) and females are relatively protected against endothelial dysfunction following salt loading compared to males (17, 22). Nonetheless, more data are needed to elucidate the role of non-osmotic Na^+ deposition in humans, and further the influence of dietary Na^+ on non-osmotic Na^+ deposition. For example, future studies are needed to determine if there are aging and racial differences in skin Na^+ with dietary salt manipulation.

Brain blood flow and sympathetic outflow

In addition to the deleterious effects of dietary salt on peripheral arteries, there is evidence that high Na^+ may adversely affect the cerebrovasculature. Classic data from INTERSALT (66) and a prospective Japanese cohort study (67) suggest that high dietary Na^+ is associated with increased mortality from strokes. Recent preclinical data from rodents suggest a high salt diet impairs cerebrovasculature function via excess inflammation and oxidative stress (68, 69). These findings are consistent with prior studies demonstrating high Na^+ reduces expression of SOD and elicits vascular dysfunction in cerebral arteries (33). Cerebral autoregulation is the ability of the brain to maintain perfusion despite changes in systemic BP and recent rodent data demonstrate short-term (three days) and chronic (four weeks) high salt impairs cerebral autoregulation (70). Taken together, these cross sectional human and experimental rodent data are important as impaired cerebrovascular dilatory responses to stimuli in humans is associated with Alzheimer's disease and stroke incidence (71). Future RCTs are needed to determine the influence of dietary salt manipulation on cerebrovascular function in humans.

Regarding the effects of salt on sympathetic outflow, salt is thought to sensitize central sympathetic circuits and excessive sympathetic outflow contributes to the development of CV disease (72). We recently demonstrated that one week of high salt alters cardiovagal baroreflex sensitivity in healthy adults (73). Elevations in plasma and cerebrospinal fluid (CSF) Na^+ enhance sympathetic nerve activity (SNA) via the rostral ventrolateral medulla (RVLM) leading to increases in BP (74). Rodent studies demonstrate that blocking SNA attenuates the BP elevations induced by high Na^+ in the CSF (74). One prior human study found that CSF Na^+ was elevated following a high salt diet in salt-sensitive and salt-resistant humans (75). However, in the group classified salt-resistant, there was a change in mean arterial BP of ~5mmHg ($_\Delta$ low to high salt diet), which many would consider to be salt-sensitive (76). Thus, more human work is needed in this area. Nonetheless, potential "sensing" mechanisms for Na^+ existing in the brain have been elucidated using rodent models (74, 77–79). Central Na^+ sensing occurs in the circumventricular organs including the organum vasculosum of the lamina terminalis (OVLT) and subfornical organ, which lack an intact blood-brain barrier (80). The OVLT has neural connections to the paraventricular nucleus of the hypothalamus, which plays an essential role in regulating SNA outflow via neuronal projections to the RVLM (81, 82). A newly published study adds additional mechanistic insight, suggesting Na_x-positive glial cells in OVLT are activated by high Na^+ concentrations, leading to enhanced hydrogen and lactate through a monocarboxylate transporter to activate ASIC1a-positive OVLT neurons (83)••.

Bone

While not typically thought of when considering CV health, bone is a target organ that may also be influenced by dietary Na^+ intake. There are data indicating high salt intake increases urinary calcium excretion, which may increase risk for osteoporosis (84). In a cross-sectional study of postmenopausal Korean women higher urinary Na^+:creatinine was positively associated with osteoporosis and negatively correlated with bone mineral density (BMD) (84). In another cross-sectional Korean study (85), urinary Na^+ excretion was negatively associated with bone mineral content (BMC) and BMD in female, but not male participants (85). In a cross-sectional study of Chinese adults urinary Na^+:K^+ was inversely associated with BMD in female, but not male participants (86). A recent meta-analysis demonstrated that higher Na^+ significantly increased the risk of osteoporosis, however there was a high degree of heterogeneity among studies (87). Lastly, a prospective observational cohort study of postmenopausal women in the U.S. Women's Health Initiative demonstrated that there was no association of dietary Na^+ intake with changes in BMD at any skeletal site (88). Collectively, these studies suggest that high dietary salt intake may be associated with impaired BMC, BMD, and risk of osteoporosis, however, there appear to be ethnicity and sex differences. Additionally, controlling for physical activity is an important consideration for studies investigating BMD and BMC. As such, additional RCTs and prospective cohort studies using more reliable estimations of Na^+ consumption (i.e., controlled feeding and multiple 24hU-Na^+ collections) are needed to elucidate the role of dietary salt on bone health.