Review

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Salt Sensitivity and Hypertension: A Paradigm Shift from Kidney Malfunction to Vascular Endothelial Dysfunction

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Hypertension is a complex trait determined by both genetic and environmental factors and is a major public health problem due to its high prevalence and concomitant increase in the risk for cardiovascular disease. With the recent large increase of dietary salt intake in most developed countries, the prevalence of hypertension increases tremendously which is about 30% of the world population. There is substantial evidence that suggests some people can effectively excrete high dietary salt intake without an increase in arterial BP, and another people cannot excrete effectively without an increase in arterial BP. Salt sensitivity of BP refers to the BP responses for changes in dietary salt intake to produce meaningful BP increases or decreases. The underlying mechanisms that promote salt sensitivity are complex and range from genetic to environmental influences. The phenotype of salt sensitivity is therefore heterogeneous with multiple mechanisms that potentially link high salt intake to increases in blood pressure. Moreover, excess salt intake has functional and pathological effects on the vasculature that are independent of blood pressure. Epidemiologic data demonstrate the role of high dietary salt intake in mediating cardiovascular and renal morbidity and mortality. Almost five decades ago, Guyton and Coleman proposed that whenever arterial pressure is elevated, pressure natriuresis enhances the excretion of sodium and water until blood volume is reduced sufficiently to return arterial pressure to control values. According to this hypothesis, hypertension can develop only when something impairs the excretory ability of sodium in the kidney. However, recent studies suggest that nonosmotic salt accumulation in the skin interstitium and the endothelial dysfunction which might be caused by the deterioration of vascular endothelial glycocalyx layer (EGL) and the epithelial sodium channel on the endothelial luminal surface (EnNaC) also play an important role in nonosmotic storage of salt. These new concepts emphasize that sodium homeostasis and salt sensitivity seem to be related not only to the kidney malfunction but also to the endothelial dysfunction. Further investigations will be needed to assess the extent to which changes in the sodium buffering capacity of the skin interstitium and develop the treatment strategy for modulating the endothelial dysfunction.

Key Words: Salt, Sensitivity, Hypertension, Kidney malfunction, Endothelial dysfunction

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Introduction

Hypertension is a complex trait determined by both genetic and environmental factors and is a major public health problem due to its high prevalence and concomitant increase in the risk for cardiovascular disease.

Among environmental factors, dietary salt intake is the

most common and important risk factor for hypertension. Salt is an essential electrolyte to the living of human beings and is used universally in cooking, seasoning, and preserving manufactured foodstuffs around the world. For several million years, human ancestors ate a diet that contained less than 1 g of salt per day. In Hunter-gathering periods, nomads hunted and ate the meat within a few hours of the kill. They do not eat salt with their food. In the mean times, population growth led to the introduction of agriculture and during the first few thousand years after the advent of agriculture, the intake of meat declined and the intake of vegetable food increased up to 90%. In this period, salt consumption in humans rose steeply. With the recent large increase of dietary salt intake in most developed countries in the world, the prevalence of hypertension increases tremendously which is about 30% of the world population[1].

Evidence from clinical observations[2,3], animal studies[4-6], clinical trials[7-12] shows a causal relation between dietary salt intake and hypertension. Many epidemiologic studies have also demonstrated that a high salt intake is associated with an increased risk of cardiovascular disease[13-16]. There is substantial evidence suggesting that blood pressure (BP) responses to dietary salt intake vary considerably among individuals which is a phenomenon described as salt sensitivity of blood pressure[17-19].

Although salt sensitivity is a well established phenomena in experimental and human hypertension, the pathophysiologic mechanisms remain unclear. It has been suggested that abnormalities in the renin angiotensin aldosterone system[20,21], the sympathetic nervous system[22], renal transmembrane sodium transport[23], the kallikrein-kinin system, the nitric oxide (NO) system, eicosanoids, and the vascular endothelium[24,25] are all involved in the pathogenesis of salt sensitive hypertension. In the evolutionary aspects, human kidneys are well-equipped with a salt retaining function and have less efficient salt excretory functions when challenged with large amounts of salt loads. If salt intake exceeds the kidney's ability to excrete salt, then it is accumulated in the body[26]. One of the main organ systems vulnerable to the adverse effects of excessive salt intake in the diet is the cardiovascular system. Excess dietary salt intake usually affects heart, blood vessels, and the kidneys. It is well documented recently that the effect of salt on BP and BP independent target organ damage goes beyond the well-known concept of Guyton[27]. Until recently, salt sensitivity of blood pressure was thought to be the result of delayed salt excretion by kidney malfunction. According to the classic concept of Guyton[26], high salt intake increases in circulating volume, which leads to a rise in perfusion pressure of the kidneys and a natriuresis that tends to restore the increased circulating volume to normal. This pressure-natriuresis mechanism prevents the increase in BP that could arise from transient increase of circulating volume. However, recent studies have added some new insights into the pathophysiologic mechanisms of salt sensitive hypertension and questioned the classic view of salt sensitivity. In this brief review, some new pieces of research related to salt sensitivity are presented[28].

The Concept of Salt Sensitivity of Blood Pressure

There is substantial evidence that blood pressure responses to dietary salt intake vary among individuals with hypertension and even with normotensive individuals. Some people can effectively excrete high dietary salt intake without an increase in arterial BP and others cannot excrete effectively without an increase in arterial BP. Former individuals who can excrete salt intake effectively are called "salt sensitive" and latter individuals who cannot are called "salt insensitive". An earlier study by Strauss et al.[29] in 1958 showed that the daily relation between dietary sodium intake and renal sodium excretion was determined in humans subjected to a step increase of salt intake from 10 to 150 mmol/day. In this study, about 5 days were required before the rate of renal sodium excretion became equal to the rate of sodium intake (ie, until sodium balance was achieved). Salt sensitivity is characterized by an alteration of kidney function that necessitates higher arterial pressure to excrete a given amount of sodium and is expressed as a reduction in the slope of the pressure-natriuresis relationship. It was shown that

the amount of sodium and water retained with such an increase of sodium intake leads to a body weight increase[30]. Unfortunately, however, there is no universal definition of salt sensitivity and the method to assess salt sensitivity varies from one study to another. In most studies, salt sensitivity is defined as the acute blood pressure change in mean blood pressure corresponding to a decrease or increase of sodium intake. In animal studies, this can be readily determined experimentally, but such measurements in humans are very difficult to perform practically. Usually, salt sensitivity is arbitrarily defined as an increase in blood pressure of 10% or greater during a high salt diet than that during a low salt diet.

In 1962, Dahl[5] demonstrated variability in blood pressure response to salt loading in normal rats. By inbreeding rats with the highest blood pressure response with rats with the lowest blood pressure response to a high-sodium intake, Dahl was able to develop two strains of rats: a salt-sensitive (SS) strain and a salt-resistant (SR) strain. The former strain becomes hypertensive with time after receiving an 8% sodium chloride diet; the latter strain does not develop hypertension in response to a high-sodium diet[5]. Similar animal study has been performed on chimpanzees, our closest relatives on a genetic basis. Chimpanzees normally consume a diet low in salt, but when their salt intake increases to that of present-day humans (~15 g/day) for 20 months, they develop hypertension. Like humans, some chimpanzees do not develop high blood pressure on a high salt diet. The rise in blood pressure was gradual and it was still rising 18 months after they started the high salt diet. Moreover, when the salt was reduced from the diet containing ~15 g salt/day to 0.5 g salt/day, blood pressure levels fell back to the original level after 6 months. It was also obvious that some chimpanzees reacted more than others to these changes of the salt intake; 60% of the cohort became hypertensive, whereas 40% remained resistant to high salt intake. Experiments in chimpanzees strongly suggested that essential hypertension is due to high salt intake[6].

In humans, Kawasaki et al. in 1978[17] were among the first to recognize a great variability in blood pressure response to sodium loading in a group of patients with essential hypertension. They studied 19 hypertensive subjects who were observed after a "normal" (109 mmol/d), "low" (9 mmol/d), and then "high" (249 mmol/d) sodium intake. Blood pressure fell significantly ($p<0.05$) in the entire population with a dietary salt restriction and increased significantly ($p<0.05$) back to baseline levels after the high salt phase. When individual blood pressure responses to the low and high salt periods alone were compared, all but one subject demonstrated an increase. The investigators then arbitrarily separated the population into two groups, identifying one as salt sensitive (n=9), those who demonstrated at least a 10% increase in mean arterial pressure when the low and high salt intake periods were compared, and the other as non-salt sensitive (n=10), those having smaller increases in blood pressure with salt loading. On the basis of this response, patients with hypertension were classified as either salt sensitive or not salt sensitive.

Next year, these observations in hypertensive patients were extended to the normotensive population by studies in individuals who were subjected to an incremental range of sodium intake from 10 to 1,500 mmol/day[18]. Luft et al.[18] in the study of 16 normotensive young men, blood pressure was measured after a 7-day period of 10 mmol/d sodium and then successive 3-day periods of 300, 600 or 800, and 1,200 or 1,500 mmol/day. Systolic and diastolic pressure increased from 113±2/69±2 mmHg (SEM) at the 10 mEq/24 hr level of sodium intake to 131±4/85±3 mmHg at the 1,500 mEq/24 hr level of sodium intake ($p<0.001$). Cardiac index increased conco- mitantly from 2.6±0.1 to 3.6±0.3 l/min/m^2 ($p<0.001$). Linear and quadratic regression analysis of the relationship of UNaV and blood pressure revealed that blacks had higher blood pressures with sodium loading than whites. Sodium loading caused a significant kaliuresis that was greater in whites than blacks. Six subjects were restudied while receiving potassium replacement. Compared with initial responses, blood pressure was elevated to a lesser degree ($p<0.02$) and a greater natriuresis appeared at a level of 1,500 mEq/24 hr of sodium intake ($p<0.02$). The data suggest that blacks have an intrinsic reduction in the ability to excrete sodium compared with whites.

Later on, Weinberger et al.[19] evaluated in 378 normotensive and 198 hypertensive humans by two approaches. Blood pressure was measured after an intravenous infusion of 2 L of normal saline (0.9%) and after sodium and volume depletion induced by a low sodium diet and furosemide administration. They arbitrarily separated the population into two groups, those in whom mean arterial blood pressure decreased by at least 10 mmHg after sodium and volume depletion were considered sodium-sensitive, and those with a decrease of 5 mmHg or less (including an increase in pressure) were considered sodium-resistant. The second study utilized the blood pressure response to modest dietary sodium restriction in 74 normotensive subjects to identify sodium sensitivity and resistance. In both studies the responses were heterogeneous. In the first study significantly more hypertensive subjects were sodium-sensitive, as compared with those in the normotensive group ($p<0.001$). Plasma renin activity (low, normal, or high) did not predict sodium responses. In both groups sodium-sensitive individuals were significantly older ($p<0.001$) and had lower baseline renin values than sodium-resistant subjects. Factors related to the change in mean arterial blood pressure after sodium and volume depletion included baseline pressure ($r=-0.54$, $p<0.001$) and age ($r=-0.16$, $p=0.002$ in the normotensive group; $r=-0.28$, $p<0.001$ in the hypertensive group). The response to dietary sodium restriction was also correlated with baseline pressure ($r=0.61$, p less than 0.001) and the initial urinary sodium excretion ($r=0.27$, $p<0.01$). Using the above criteria, 51% of hypertensives and 26% of normotensives were found to be sodium sensitive in this study. They also conducted this protocol twice within 12 months in additional subjects and observed the blood pressure responses[31]. The blood pressure response was reproducible in 28 subjects studied twice ($r=0.56$, $p<0.002$). Four subjects changed salt-responsiveness status and six were indeterminate on restudy. In a subsequent study these investigators also showed that the blood pressure response to the volume expansion-contraction protocol significantly correlated with the changes in blood pressure observed in response to a low-sodium diet[32]. This is the only published study to have compared two different techniques for the assessment of salt responses of blood pressure in the same persons. They concluded that salt sensitivity is a reproducible phenomenon that is related to the age-associated increase in blood pressure. Since then, a variety of protocols have been used to test for the salt sensitivity of BP in humans, including the examination of the BP response to an acute protocol in which patients are salt-loaded with an intravenous infusion of saline and salt-depleted by administration of furosemide[33,34].

In the GenSalt study[35], participants received a low-sodium diet (3 g of salt or 51.3 mmol of sodium per day) for 7 days followed by a high-sodium diet (18 g of salt or 307.8 mmol of sodium per day) for 7 days, with BP measured three times during the last 3 days of each intervention phase. BP responses to chronic low- and high-sodium dietary interventions, usually lasting 5-14 days, were also measured. The overall objective of this study is to identify susceptibility genes that influence individual BP responses to dietary sodium and potassium intake in human populations. BP response to dietary sodium intake varies among individuals- a phenomenon described as salt sensitivity- and the heterogeneity of this effect is far from being completely understood[17,33]. Previous prospective cohort studies have also indicated that salt sensitivity is a strong predictor for CVD and total mortality in hypertensive and normotensive participants[36,37]. The GenSalt study group examined BP responses to dietary sodium and potassium interventions by sex, age, and baseline BP subgroups among 1906 Chinese men and women aged 16 years or older who participated in the Genetic Epidemiology Network of Salt Sensitivity (GenSalt)[38]. This study showed that female gender, older age, and elevated baseline BP levels increase BP responses to dietary sodium intervention. In addition, elevated baseline BP levels increase BP responses to dietary potassium intervention. Therefore, a diet low in sodium and high in potassium should be especially effective in reducing BP among persons with hypertension or prehypertension, whereas a diet low in sodium may be more effective in reducing BP among women and the elderly[38]. Six years later, Gu et al. in their

GenSalt study, retested BP responses to dietary sodium and potassium interventions among previous 487 participants[39]. This is the first study to investigate the long-term reproducibility of salt sensitivity of BP. The identical dietary intervention protocol, which included a 7-day low-sodium feeding (51.3 mmol/d), a 7-day high- sodium feeding (307.8 mmol/d), and a 7-day high-sodium feeding with oral potassium supplementation (60.0 mmol/ d), was applied in both the initial and repeated studies. Three blood pressure measurements were obtained during each of the 3 days of baseline observation and on days 5, 6, and 7 of each intervention period. The results from the 24-hour urinary excretion of sodium and potassium showed excellent compliance with the study diet. Blood pressure responses to dietary intervention in the original and repeated studies were highly correlated. The correlation coefficients (95% confidence interval) for systolic blood pressure levels were 0.77 (0.73-0.80) at baseline, 0.79 (0.75-0.82) during low sodium, 0.80 (0.77-0.83) during high sodium, and 0.82 (0.79-0.85) during high sodium and potassium supplementation interventions (all, $p< 0.0001$). The correlation coefficients for systolic blood pressure changes were 0.37 (0.29-0.44) from baseline to low sodium, 0.37 (0.29-0.44) from low to high sodium, and 0.28 (0.20-0.36) from high sodium to high sodium plus potassium supplementation (all, $p<0.0001$). These data indicate that blood pressure responses to dietary sodium and potassium interventions have long-term repro ducibility and stable characteristics in the general population. However, de Leeuw and Kroon[40] in their editorial comment argue that the correlation coefficients for the pressure changes at the beginning and the end of the study were very low. The initial test results can only explain about 20% of the results from the retest.

Pathophysiologic Mechanisms of Salt Sensitivity of Blood Pressure

Traditional views

A considerable amount of work has accumulated and decades of research uncovered a myriad of mechanisms and the pivotal role of the kidney in its pathogenesis of hypertension.

In 1963, Borst and Borst-de Geus[41] postulated that "hypertension is part of a homeostatic reaction to deficient renal sodium output." Various mechanisms relating to salt intake and blood pressure elevation have been proposed over the last several decades. In the 1970s, animal experiments by Dahl on rats suggested that hypertension associated with increased dietary sodium intake reflected an intrinsic defect in the renal excretion of sodium. When the kidney from a salt-sensitive rat was transplanted into a salt-resistant rat, the recipient developed hypertension. Conversely, when a kidney from a salt-resistant rat was transplanted into a salt-sensitive rat, the hypertension resolved[42]. Salt sensitivity of BP refers to the BP responses to changes in dietary salt intake to produce meaningful BP increases or decreases.

Nearly five decades ago, Guyton and Coleman[43] proposed that if an increase in arterial pressure could produce sustained elevations in urine flow and sodium excretion through the mechanism of pressure diuresis, then the system would have an infinite gain for the long-term control of arterial pressure by regulating blood volume. Whenever arterial pressure is elevated, pressure natriuresis enhances the excretion of sodium and water until blood volume is reduced sufficiently to return arterial pressure to control values. According to this hypothesis, hypertension can develop only when something impairs the excretory ability of the kidney and shifts the relation between sodium excretion and arterial pressure toward higher values[44]. They showed the integral role of kidney in blood pressure regulation. Recently, a genetic cause for salt sensitivity has been vigorously pursued with a particular focus on the kidney and indeed, mutations in a large number of genes related to salt transport in the kidney have been shown to cause monogenic forms of hypertension[45].

The molecular mechanism of renal handling of salt-sensitive hypertension has been also newly developed. Fugita et al.[46,47] recently identified two novel pathways in salt-sensitive hypertension: the β2-adrenergic stimulant-gluco-

corticoid receptor (GR)-with-no-lysine kinase (WNK)4-Na^+-Cl^- cotransporter pathway, which is active in distal convoluted tubule (DCT)1, and the Ras-related C3 botulinum toxin substrate (Rac)1-mineralocorticoid receptor pathway, which is active in DCT2, connecting tubules, and collecting ducts. They suggested that these new pathways might be novel therapeutic targets for the treatment of salt-sensitive hypertension and new diagnostic tools for determining the salt sensitivity of hypertensive patients.

Nonosmotic Sodium Accumulation and Salt Sensitivity

On the contrary to Guyton's traditional view, Heer et al. in 2,000 performed a controlled randomized study including 32 healthy males. Study subjects were randomized into four groups, each ingesting 50, 200, 400, and 550 mEq/day of NaCl for 7 days. In this study, plasma volume dose dependently increased but total body water did not. They concluded that in contrast to the traditional view, high sodium intake does not induce total body water storage but induces a relative fluid shift from the interstitial into the intravascular space[48]. Dietary salt intake and extracellular fluid volume expansion is traditionally seen as a balance between salt intake and excretion, and the osmotic balance between the extracellular and intracellular spaces. This paradigm assumes that sodium and its accompanying anion are osmotically active and retained with water in amounts that leave osmolality unchanged. However, Heer et al.'s results were not fit for traditional view and led the authors to consider a nonosmotic sodium storage occurring in the subjects ingesting high salt intakes.

Recently, Titze et al. in their rat experiment have shown that sodium may accumulate without accompanying water retention and that the skin is a major site for osmotically inactive sodium storage[49]. Negatively charged glycosaminoglycans under the skin function as sodium binders[50]. Nonosmotic sodium accumulation in the interstitium explains the observations of positive sodium balance without concomitant osmotic volume expansion. Nonosmotic sodium accumulation occurs acutely and is presumably followed by increased removal from skin via the newly developed lymphatics for ultimate renal excretion. Machnik et al. showed that mice and rats receiving a high-salt diet developed hypertonicity of the skin interstitium, which triggered a series of mechanisms to keep interstitial volume constant[51,52]. The hypertonic sodium accumulation resulted in the activation of the tonicityresponsive enhancer binding protein (TonEBP) present in mononuclear cells infiltrating the skin. As a consequence, these skin macrophages secreted vascular endothelial growth factor (VEGF)-C resulting in increased density and hyperplasia of the skin lymphocapillary network and increased endothelial nitric oxide synthase (eNOS). Our traditional view of sodium handling has been challenged by these studies[49-52].

Endothelial Surface Layer - Another Important Sodium Barrier and Storage Site

Recently, the endothelial surface layer facing the blood stream may be another important non-osmotic sodium storage compartment. This soft surface layer, termed endothelial glycocalyx layer (EGL) that coats the luminal surface of endothelium, is a negatively charged biopolymer known to preferentially bind sodium. At present, the sodium binding capacity of the EGL is not known. However, the negative charge of the entire vascular EGL in humans have been calculated to be able to inactivate about 700 mg of sodium, which is about the amount contained in a single meal[53]. These calculations are on the basis of in vitro experiments and most likely underestimate EGL dimensions. In vivo, the actual EGL volume has 7-30 times larger than in vitro experiments. Under normal physiologic conditions, the EGL may be able to inactivate more sodium than in vitro calculated sodium amount[54,55]. Oberleithner et al. showed that sodium excess leads to the deterioration of the EGL, and the damaged EGL facilitates sodium entry into the endothelial cells[56]. These results could explain endothelial dysfunction and arterial hypertension observed in sodium abuse. This study suggested that the sodium buffering capacity

of the endothelial glycocalyx is severely damaged by excessive sodium intake over time, leading to a signifi- cant reduction of the negatively charged heparan sulphate residues in the endothelial glycocalyx[56]. A plasma sodium concentration in the high physiological range (>140 mM) reduces the negatively charged heparan sulphate residues of the endothelial glycocalyx, increasing the amount of sodium reaching the endothelial sodium channels, which in turn makes the channels more active[57,58].

Endothelial surface layer also has been reported to influence on the availability of NO production via mediating the epithelial sodium channel on the endothelial luminal surface (EnNaC). When the plasma sodium was increased, the density of EnNaC has been shown to be increased to leading to increasing sodium uptake, stiffen the endothelial cellular cortex, and diminishing NO production. Taken together, an increase of sodium delivery to the endothelial cell resulted in an increase in vascular tone[58,59]. Recent study showed that the inhibitory feedback mechanism of sodium on ENaC activity in kidney and the feedforward mechanism of sodium on EnNaC in vascular endothelium could be complementary processes for Na^+ homeostasis and blood pressure regulation. In the vascular endothelium, an acute increase of extracellular sodium concentration could induce a fast aldosterone- and mineralocorticoid receptor-dependent insertion of EnNaC into the plasma membrane which led to reduce NO release. However, when the rise in plasma sodium/aldosterone might persist, a pathophysiological response which the vascular stiffness was increased and the release of NO was diminished finally led to endothelial dysfunction accompanied by structural damage of the endothelium[60,61].

Conclusions

It is well known that excess salt intake is definitely associated with hypertension in some but not all individuals. Salt sensitivity of BP refers to the BP responses for changes in dietary salt intake to produce meaningful BP increases or decreases. The underlying mechanisms that promote salt sensitivity are complex and range from genetic to environmental influences. The phenotype of salt sensitivity is therefore heterogeneous with multiple mechanisms that potentially link high salt intake to increases in blood pressure. Moreover, excess salt intake has functional and pathological effects on the vasculature that are independent of blood pressure. Epidemiologic data demonstrate the role of high dietary salt intake in mediating cardiovascular and renal morbidity and mortality.

Almost five decades ago, Guyton and Coleman[43] proposed salt sensitivity to be the result of kidney malfunction. However, recent studies suggest that nonosmotic salt accumulation in the skin interstitium and changes in endothelial surface layer characteristics which lead to alteration of endothelial cell function also play an important role in nonosmotic storage of salt. These new concepts emphasize that sodium homeostasis and salt sensitivity seem to be related not only the kidney malfunction but also the endothelial dysfunction.

Further investigations will be needed to assess the extent to which changes in the sodium buffering capacity of the skin interstitium and develop the treatment strategy for the amelioration of endothelial dysfunction.

Conflicts of Interest

The authors have no conflicts of interest.

References

1. Wolf-Maier K, Cooper RS, Banegas JR, et al.: Hypertension prevalence and blood pressure in 6 European countries, Canada, and the United States. JAMA 289:2363-2369, 2003
2. Ambard L, Beaujard E: Causes de l=hypertension artérielle. Arch Gen Med 1:520-533, 1904
3. Kempner W: Treatment of hypertensive vascular disease with the rice diet. Am J Med 4:545-577, 1948
4. Ball OT and Meneely GR: Observations on dietary sodium chloride. J Am Diet Assoc 33:366-370, 1957
5. Dahl LK, Heine M, Tassinari L: Effects of chronic salt ingestion. Evidence that genetic factors play an important role in susceptibility to experimental hypertension. J Exp Med 115:1173-1190, 1962
6. Denton D, Weisinger R, Mundy NI, et al.: The effect

of increased salt intake on blood pressure of chimpanzees. Nat Med 1:1009-1016, 1995
7. MacGregor GA, Markandu ND, Best FE, et al.: Double-blind randomised crossover trial of moderate sodium restriction in essential hypertension. Lancet 1:351-355, 1982
8. Intersalt Cooperative Research Group: Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 h urinary sodium and potassium excretion. BMJ 297:319-328, 1988
9. The Trials of Hypertension Prevention Collaborative Research Group: The effects of nonpharmacologic interventions on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. JAMA 267:1213-1220, 1992
10. The Trials of Hypertension Prevention Collaborative Research Group: Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure: the Trials of Hypertension Prevention, phase II. Arch Intern Med 157:657-667, 1997
11. Whelton PK, Appel LJ, Espeland MA, et al. for the TONE Collaborative Research Group: Sodium reduction and weight loss in the treatment of hypertension in older persons. A randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). JAMA 279:839-846, 1998
12. Sacks FM, Svetkey LP, Vollmer WM, et al.: DASH-Sodium Collaborative Research Group: Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med 344:3-10, 2001
13. He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK: Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. JAMA 282:2027-2034, 1999
14. Tuomilehto J, Jousilahti P, Rastenyte D, et al.: Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. Lancet 357:848-851, 2001
15. Cook NR, Cutler JA, Obarzanek E, et al.: Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow up of the trials of hypertension prevention (TOHP). BMJ 334:885-888, 2007
16. Strazzullo P, D'Elia L, Kandala N-B, Cappuccio FP: Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ 339:b4567-b4576, 2009
17. Kawasaki T, Delea CS, Bartter FC, Smith H: The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. Am J Med 64:193-198, 1978
18. Luft FC, Rankin LI, Bloch R, et al.: Cardiovascular and humoral responses to extremes of sodium intake in normal black and white men. Circulation 60:697-706, 1979
19. Weinberger MH, Miller JZ, Luft FC, Grim CE, Fineberg NS: Definitions and characteristics of sodium sensitivity and blood pressure resistance. Hypertension 8(suppl 2): II127-II134, 1986
20. Luft FC, Weinberger MH: Sodium sensitivity and resistance of blood pressure: the role of the kidney and the renin-aldosterone axis. Kidney Int 22(Suppl):S234-S241, 1987
21. Giner V, Poch E, Bragulat E, et al.: Renin-angiotensin system genetic polymorphisms and salt sensitivity in essential hypertension. Hypertension 35:512-517, 2000
22. De la Sierra A, Lluch MM, Coca A, et al.: Fluid, ionic and hormonal changes induced by high salt intake in salt-sensitive and salt-resistant hypertensive patients. Clin Sci 91:155-161, 1996
23. Lluch MM, De la Sierra A, Poch E, et al.: Erythrocyte sodium transport, intraplatelet pH, and calcium concentration in salt sensitive hypertension. Hypertension 27: 919-925,1996
24. Miyoshi A, Suzuki H, Fujiwara M, Masai M, Iwasaki T: Impairment of endothelial function in salt-sensitive hypertension in humans. Am J Hypertens 10:1083-1090, 1997
25. Bragulat E, De la Sierra A, Antonio MT, Coca A: Endothelial dysfunction in salt-sensitive hypertension. Hypertension 37:444-448, 2001
26. Guyton AC: Blood pressure control-special role of the kidneys and body fluids. Science 252:1813-1816, 1991
27. Farquhar WB, Edwards DG, Jurkovitz CT, Weintraub WS: Dietary sodium and health. More than just blood pressure. J Am Col Cardiol 65:1042-1050, 2015
28. Kusch-Vihrog K, Oberleithner H: An emerging concept of vascular salt sensitivity. F1000 Biology Reports 4:20-26, 2012
29. Strauss MB, Lamdin E, Smith WP, et al.: Surfeit and deficit of sodium: a kinetic concept of sodium excretion. Arch Intern Med 102:527-536, 1958
30. Reineck JH, Stein JH. Regulation of sodium balance. In: Maxwell MH, Kleeman CR, eds. Clinical disorders of fluid and electrolyte metabolism. New York: McGraw-Hill, 1980, p89-112

31. Weinberger MH, Fineberg NS: Sodium and volume sensitivity of blood pressure: Age and pressure change over time. Hypertension 18:67-71, 1991
32. Weinberger MH. Stegner JE, Fineberg NS: A comparison of two tests for the assessment of blood pressure responses to sodium. Am J Hypertens 6:179-184, 1993
33. Weinberger MH: Salt sensitivity of blood pressure in humans. Hypertension 27:481-490, 1996
34. Luft FC, Weinberger MH: Heterogeneous responses to changes in dietary salt intake: the salt sensitivity paradigm. Am J Clin Nutr 65:612S-617S, 1997
35. GenSalt Collaborative Research Group: GenSalt: rationale, design, methods and baseline characteristics of study participants. J Hum Hypertens 21:639-646, 2007
36. Morimoto A, Uzu T, Fujii T, et al.: Sodium sensitivity and cardiovascular events in patients with essential hypertension. Lancet 350:1734-1737, 1997
37. Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M: Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. Hypertension 37:429-432, 2001
38. He J, Gu D, Chen J, et al.: Gender difference in blood pressure responses to dietary sodium intervention in the GenSalt study. J Hypertens 27:48-54, 2009
39. Gu D, Zhao Q, Chen J, et al.: Reproducibility of Blood Pressure Responses to Dietary Sodium and Potassium Interventions. The GenSalt Study. Hypertension 62:499-505, 2013
40. de Leeuw PW, Kroon AA: Salt and sensitivity. Hypertension. 62:461-462, 2013
41. Borst JG, Borst-de Geus A: Hypertension explained by Starling's theory of circulatory homeostasis. Lancet 1: 677-682, 1963
42. Dahl LK, Heine M, Thompson K: Genetic influence of the kidneys on blood pressure. Evidence from chronic renal homografts in rats with opposite predispositions to hypertension. Circ Res 34:94-101, 1974
43. Guyton AC, Coleman TG. Long-term regulation of the circulation: inter-relationship with body fluid volumes. In: Reeve E, Guyton AC, eds. Physical basis of circulatory transport: regulation and exchange. Philadelphia: Saunders, 1967:179-201
44. Cowley AW Jr.: Long-term control of arterial blood pressure. Physiol Rev 72:23l-300, 1992
45. Lifton R, Gharavi AG, Geller DS: Molecular mechanisms of human hypertension. Cell 104:545-556, 2001
46. Mu S, Shimosawa T, Ogura S, et al.: Epigenetic modulation of the renal β-adrenergic-WNK4 pathway in salt-sensitive hypertension. Nat Med 17:573-580, 2011
47. Nishimoto M, Fujita T: Renal mechanisms of salt-sensitive hypertension: contribution of two steroid receptor-associated pathways. Am J Physiol Renal Physiol 308: F377-387, 2015
48. Heer M, Baisch F, Kropp J, Gerzer R, Drummer C: High dietary sodium chloride consumption may not induce body fluid retention in humans. Am J Physiol Renal Physiol 278:F585-F595, 2000
49. Titze J, Bauer K, Schafflhuber M, et al.: Internal sodium balance in DOCA-salt rats: A body composition study. Am J Physiol Renal Physiol 289:F793-F802, 2005
50. Titze J, Shakibaei M, Schafflhuber M, et al.: Glycosa minoglycan polymerization may enable osmotically inactive Na^+ storage in the skin. Am J Physiol Heart Circ Physiol 287:H203-H208, 2004
51. Machnik A, Neuhofer W, Jantsch J, et al.: Macrophages regulate salt dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. Nat Med 15:545-552, 2009
52. Machnik A, Dahlmann A, Kopp C, et al.: Mononuclear phagocyte system depletion blocks interstitial tonicity-responsive enhancer binding protein/vascular endothelial growth factor C expression and induces salt-sensitive hypertension in rats. Hypertension 55:755-761, 2010
53. Oberleithner H: Two barriers for sodium in vascular endothelium? Ann Med 2012
54. Potter DR, Jiang J, Damiano ER: The recovery time course of the endothelial cell glycocalyx in vivo and its implications in vitro. Circ Res 104:1318-1325, 2009
55. Chappell D, Jacob M, Paul O, et al.: The glycocalyx of the human umbilical vein endothelial cell: An impressive structure ex vivo but not in culture. Circ Res 104:1313-1317, 2009
56. Oberleithner H, Peters W, Kusche-Vihrog K, et al.: Salt overload damages the glycocalyx sodium barrier of vascular endothelium. Pflugers Arch 462:519-528, 2011
57. Oberleithner H, Riethmuller C, Schillers H, MacGregor GA, de Wardener HE, Hausberg M: Plasma sodium stiffens vascular endothelium and reduces nitric oxide release. Proc Natl Acad Sci USA 104:16281-6, 2007
58. Korte S, Wiesinger A, Straeter AS, Peters W, Oberleithner H, Kusche-Vihrog K: Firewall function of the endothelial glycocalyx in the regulation of sodium homeostasis. Pflugers Arch 463:269-278, 2012

59. Olde Engberink RH, Rorije NM, Homan van der Heide JJ, van den Born BJ, Vogt L: Role of the vascular wall in sodium homeostasis and salt sensitivity. J Am Soc Nephrol 26:777-783, 2015
60. Korte S1, Sträter AS1, Drüppel V1, Oberleithner H1, Jeggle P1, Grossmann C2, et al.: Feedforward activation of endothelial ENaC by high sodium. FASEB J 28:4015-4025, 2014
61. Lang, F: Stiff endothelial cell syndrome in vascular inflammation and mineralocorticoid excess. Hypertension 57:146-147, 2011