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Commentary

# Evaluation of the pathophysiological mechanisms of salt sensitivity

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Globally, hypertension is estimated to affect 40% of adults and cause 7.5 million deaths, approximately 12.8% of all deaths [1]. And the rate of hypertension control is still exceptionally low. There is strong evidence to suggest a causal relationship between salt intake and high blood pressure. Salt sensitivity is an independent risk factor for cardiovascular disease (CVD) and mortality, which is present in half of the hypertensive population and one quarter of the normotensive subjects [2,3]. Additionally, despite the unquestionable influence of environmental factors in the determination of salt sensitivity in humans, estimates of its heritability have been as high as 74% in blacks and 50% in Chinese subjects, both higher than those for hypertension [4].

Salt sensitivity is especially frequent in normotensives from subpopulations known to have a higher frequency of hypertension, such as blacks, older subjects, and first-degree relatives of hypertensives, suggesting that salt sensitivity is a predictor of hypertension [4,5]. Investigating the causes of salt sensitivity will contribute to finding new drugs for hypertension. With respect to the pathophysiology of salt sensitivity, the relative roles of abnormal vascular resistance responses to salt loading [6-9] versus abnormal sodium-volume responses to salt loading [10-13] are controversial. Most studies in normotensive subjects have indicated that the initiation of salt-induced hypertension usually involves abnormal vascular resistance responses to increased salt intake, not greater renal retention of a salt load in salt-sensitive normotensive subjects than in salt-resistant normotensive controls [14-18]. Salt sensitive hypertensive subjects also do not retain more of a salt load than salt resistant normotensive controls [19], although they may retain more of a salt load than salt-resistant hypertensive subjects [20].

According to the Guyton theory, kidney plays the central role in the regulation of blood pressure (BP) via renal pressure natriuresis. He provides a framework that could be adapted to future findings, in which a high-salt diet engenders sodium accumulation, volume expansion, cardiac output adjustments, and then autoregulation for flow maintenance are involved. According to the Guyton theory, an abnormal increase in the amount of renal salt reabsorption/retention is usually an early, critical abnormality that enables increased salt intake to initiate hypertension [21]. However, in a series of carefully performed studies, Greene et al. clearly showed that increased dietary salt intake expanded blood volume and increased cardiac output (CO) in the Brookhaven strains of both Dahl salt sensitive (SS) and salt resistant (SR) rats, but only in the SS rats did BP increase [11]. Consistent with the clinical study, Luft et al. [21,22] showed that high salt intake increased CO and decreased peripheral vascular resistance (PVR) in normotensive men. Schmidlin et al. [14,15] also observed, despite similar increases in CO and cumulative sodium balance, that SS but not SR individuals manifested salt-induced increases in mean arterial pressure. The SR volunteers showed rapid reductions in calculated systemic vascular resistance (SVR), whereas SVR did not decline and actually increased over time in the SS patients. These data suggest that the ability of individuals to respond with an appropriate vasodilatory response to increased salt intake is pivotal.

In Guyton's era, nitric oxide (NO) and natriuretic peptides were unknown and prostaglandin function had only been sketchily outlined. The vascular stress dilation is not well known. Two excellent reviews have discussed the effects of NO on renal epithelial cell regulation of salt and

water balance [23], renal hemodynamics [24] and the relationship with arterial pressure. Roman [25] showed a rightward shift in the pressure-natriuresis curve in prehypertensive Dahl SS rats. This defect in pressure-natriuresis was repaired by chronic administration of L-arginine [26]. NOS polymorphism and decreased NOS activity is reported common in blacks or aging people, who are high in the prevalence of salt-sensitive hypertension [27-29]. Salt-sensitive individuals release less NO during NO agonist administration compared with salt-resistant essential hypertension individuals [30]. Theses indicate that NO plays a vital role in salt sensitivity.

NO in the kidney could be derived from any isoform of NO synthase (NOS) [22]. It has been reported that NO derived from neuronal nitric oxide synthase (nNOS) plays a role in the regulation of afferent arteriolar diameter and long- and short-term tubule glomerular feedback [31]. Whole body eNOS knockout mice showed a high basal mean BP (125 ± 4 mm Hg) with a further increase in BP after excess salt intake [32]. Therefore, we used low-dose N-nitro-L-arginine Methyl Ester (L-NAME) to systemically inhibit all subunits of NOS to induce salt sensitivity. The dose of L-NAME does not elevate blood pressure per se nor induce renal fibrosis. Other studies revealed that high dose L-NAME (25 mg/kg/day of L-NAME, 25 times higher than what we have used) could induce salt-sensitive hypertension even after cessation of L-NAME [33,34]. But that model causes severe renal parenchymal fibrosis and possibly impairs renal sodium handling secondary to fibrosis. They suggested that renal damage and activation of renin-angiotensin axis [34] are the causes of salt-sensitive hypertension in that model. In our former study, we showed no apparent renal parenchyma damage, whilst keeping the rodents normotensive unless high-salt diet is given. The results suggest that this low dose of L-NAME induces salt-sensitivity in normotensive animals even in the absence of renal parenchymal damage [35].

During the first 24 hours of salt loading, blood volume increased to the same extent in the LNAME-treated group and control group. However, blood pressure increased only in the LNAME group. The blood pressure changes appear earlier than that in blood volume. This finding demonstrated that elevated blood volume is not sufficient for the initiation of hypertension. The results raise the possibility that within the first 24 hours of salt loading, the L-NAME+HS animals failed to normally vasodilate and reduce systemic vascular resistance in response to the salt-loading and blood volume expansion. In contrast, the normal controls may have responded to the same degree of salt-induced volume expansion by vasodilating and reducing systemic vascular resistance which prevents the salt-induced increases in blood volume from increasing blood pressure. We revealed that by using this model, although the circulating blood volume is comparable between salt-sensitive and salt-resistant rodents, only the salt-sensitive model developed hypertension within 24 hours on a high salt diet. The results highly suggested that elevated blood volume is not sufficient for initiation of the salt-sensitive hypertension on a day after high salt intake. It suggests that a failure of vasodilatation in response to volume expansion induces salt sensitivity. Kurtz et al. contend Guyton hypothesis that instead of a natriuretic shortcoming, the problem is vascular dysfunction in the form of a failure to reduce peripheral resistance to accommodate the increased volume that provokes the BP rise in salt sensitivity [36-38]. And the decrease in blood volume was associated with an increase in urinary sodium excretion, which is consistent with data in human. It suggests that to maintain salt-sensitive hypertension, sodium retention and increases in blood volume are necessary.

L-NAME changes renal blood flow [39] and to exclude the microenvironment changes in the kidney, we examined the effect of L-NAME and NO in vitro using mDCT cells in which eNOS is expressed. Blockade of NO in mDCT cells with L-NAME and treatment with sodium nitroprusside (SNP) altered phosphorylation of thiazide-sensitive sodium-chloride co-transporter (NCC) and these data suggest that NO interacts with phosphorylation of NCC. It is well known that L-NAME results in high oxidative stress [40], a result which was also confirmed by analyzing superoxide levels in the present study. After co-treatment with a superoxide dismutase (SOD) mimetic TEMPO, the L-NAME-induced increases in p-NCC was downregulated. pSPAK, a classic activator of NCC, phosphorylate NCC at conserved Ser/Thr residues in the cytoplasmic N-terminal domain [41]. In the study, the expression of pSPAK was also increased by L-NAME stimulation and downregulated by TEMPO + L-NAME co-treatment in mDCT cells. At the same time, NO donor decreased superoxide levels and pSPAK expression in mDCT cells. To confirm the role of pSPAK, we inhibited pSPAK and subsequently demonstrated the failure of L-NAME to activate NCC in the presence of a pSPAK inhibitor. Furthermore, we demonstrated the role of ROS in NO-induced salt-sensitive hypertension *in vivo*. After 4 weeks of treatment, TEMPO attenuated the L-NAME- and salt-induced increases in superoxide levels, mean BP and p-NCC expression in the C57BL/6J mice. These results indicate that oxidative stress and pSPAK play a role in the interaction between NO and NCC.

However, in our study, we did not measure the serum sodium balance. Although we observed that a decrease in blood volume was associated with an increase in urinary sodium excretion in salt resistant group, and there is a sodium retention in salt sensitive group. Where is the excessive sodium loss, is still unclear? Guyton's hypothesis is based on the premise that all mechanisms of salt handling are geared toward maintaining sodium excretion parallel to sodium intake (ie, achieving constant salt balance). However, it has been reported recently that healthy humans are able to osmotically inactivate a significant proportion of sodium after an infusion of hypertonic saline [22,42]. Recent observations by Laffer question this conventional knowledge: sodium can be stored in hyperosmolar concentrations (or at least without iso-osmolar water) in certain tissues such as skin and muscle, with a behavior different from that in the extracellular space [43]. This osmotically inactive sodium storage could therefore serve as a mechanism for buffering volume and blood pressure following changes in salt intake [44]. Skin sodium appears to be higher in older individuals, which previously was known to have the salt sensitivity trait. Titze et al. showed that skin sodium changes during dialysis support its role as a buffer system [18,21-22]. Higher skin sodium storage in aging is associated with higher BP and target organ damage. The possible mechanism involves VEGF-C, which determines skin sodium in aging, potentially via lymphangiogenesis, facilitating the efflux of sodium [38].

In this COVID-19 pandemic era, the vascular dysfunction is more often observed than before. Postmortem examination of COVID-19 patients reveals that virus-like particles were present in endothelial cells and proximal tubular epithelial cells [45], which indicate a high probability to develop salt sensitivity. As COVID-19 virus induces cytokine-storm and damages vascular endothelial cells and renal tubules. The COVID-19 survivors are reported to have

several left-over symptoms such as dyspnea and dysgeusia. Although there is no survey on newly diagnosed hypertension among COVID-19 survivors, the endothelial damages last for several month and when survivors take high salt diet, they may develop salt-sensitive hypertension. The health care providers should pay high attention to reduce salt intake and keep eyes on blood pressure.

In conclusion, mild impairment of NO activity might be an important determinant of vascular resistance and blood volume responses to salt loading that mediate the initiation and maintenance of salt-induced hypertension. Certainly, more work is needed to understand the underlying pathobiology of the effects of high salt in the context of salt sensitive hypertension.

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