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Key Points:

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Salt sensitive hypertension is a major risk factor for cardiovascular morbidity and mortality. The pathophysiological mechanisms leading to different individual blood pressure responses to changes in dietary salt remain elusive. Research in the last two decades revealed that the immune system plays a critical role in the development of hypertension and related end organ damage. Moreover, sodium accumulates nonosmotically in human tissue including skin and muscle, shifting the dogma on body sodium balance and its regulation. Emerging evidence suggest that high concentrations of extracellular sodium can directly trigger an inflammatory response in antigen presenting cells (APCs), leading to hypertension and vascular and renal injury. Importantly, sodium entry into APCs is mediated by epithelial sodium channel (ENaC). While the role of ENaC in renal regulation of sodium excretion and blood pressure is well-established, these new findings imply that ENaC may also exert blood pressure modulatory effects in extrarenal tissue through an immune-dependent pathway. In this review, we discuss the recent advances in our understanding of the pathophysiology of salt sensitive hypertension with a particular focus on the roles of APCs and extrarenal ENaC.

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Dendritic Cell ENaC in Inflammation, Salt-sensitive Hypertension and Kidney Damage

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Abstract
Salt sensitive hypertension is a major risk factor for cardiovascular morbidity and mortality. The pathophysiological mechanisms leading to different individual blood pressure responses to changes in dietary salt remain elusive. Research in the last two decades revealed that the immune system plays a critical role in the development of hypertension and related end organ damage. Moreover, sodium accumulates nonosmotically in human tissue including skin and muscle, shifting the dogma on body sodium balance and its regulation. Emerging evidence suggest that high concentrations of extracellular sodium can directly trigger an inflammatory response in antigen presenting cells (APCs), leading to hypertension and vascular and renal injury. Importantly, sodium entry into APCs is mediated by epithelial sodium channel (ENaC). While the role of ENaC in renal regulation of sodium excretion and blood pressure is well-established, these new findings imply that ENaC may also exert blood pressure modulatory effects in extrarenal tissue through an immune-dependent pathway. In this review, we discuss the recent advances in our understanding of the pathophysiology of salt sensitive hypertension with a particular focus on the roles of APCs and extrarenal ENaC.
Introduction

Hypertension is a major cause of cardiovascular and renal disease affecting approximately 30% of the adult population. The pathophysiological mechanisms underlying the development of essential hypertension are complex, involving both environmental and genetic factors. Dysfunction in multiple organ systems is implicated, including kidneys, vasculature and central nervous system. Research in the last two decade has further established the immune system as a key player in the pathogenesis of hypertension.

Cells of both the innate and adaptive immune systems play important roles in the development of hypertension and kidney damage. Antigen presenting cells (APCs) are crucial for the initiation of the inflammatory process in response to hypertensive stimuli. APCs include primarily dendritic cells (DCs), which are the most potent antigen presenters, as well as macrophages and B cells. These cells initiate T cell activation through antigen-MHC receptor complex while also expressing co-stimulatory molecules and cytokines to orchestrate the immune response. Importantly, various pro-hypertensive stimuli, such as dietary salt, angiotensin II (Ang II) and catecholamines have been shown to promote the infiltration of APCs and T cells in the vasculature and kidneys, where their activation incite endothelial damage and renal injury seen in hypertension.

The relationship between sodium (Na\(^+\)), a major hypertensive stimulus, and blood pressure is mainly dependent on the salt sensitivity of an individual. Salt sensitivity of blood pressure, in which changes in dietary salt intake is accompanied by parallel changes in blood pressure, affects more than half of all hypertensive patients and constitutes an additional risk factor for cardiovascular mortality and renal disease in this population. This observation is particularly of interest given that the average Na\(^+\) intake is approximately 2 to 3 times of the recommended maximum in most countries.
Latest research suggests that inflammation may mediate the hypertensive effects of salt. Our understanding of body Na⁺ homeostasis and salt sensitivity has been reshaped following the discovery that Na⁺ accumulates in the interstitium of tissue without commensurate water retention ¹², ¹³. The discovery of this nonosmotic Na⁺ storage is of paramount importance since recent animal studies suggest that APCs can be activated by high concentrations of extracellular Na⁺ via an epithelial Na⁺ channel (ENaC)-dependent pathway, which leads to T cell activation and end organ damage in hypertension ¹⁴. In this review, we will provide an overview of the current findings relating to the roles of extrarenal ENaC activity and APC-initiated inflammatory response in salt sensitive hypertension.

Pathophysiology of salt sensitive hypertension

The mechanisms of salt sensitive hypertension remain controversial. The traditional concept suggested by Guyton et al. hypothesized that salt sensitive individuals have dysfunctional renal Na⁺ handling. Based on this concept, a salt load would increase plasma volume until isosmotic balance is reached, which would lead to pressure-natriuresis and renal salt excretion, bringing blood pressure to the baseline level ¹⁵. Hence, only a defect in renal natriuretic system would explain a salt induced elevation in blood pressure. Indeed, extensive research has found various alterations in renal Na⁺ channels ¹⁶-¹⁹, renin angiotensin system ²⁰-²², and sympathetic syste ²³-²⁶ in salt sensitive hypertension. Nevertheless, the precise pathogenesis of salt sensitivity remains controversial. Importantly, hemodynamic studies after salt loading and depletion showed no difference in Na⁺ balance and plasma volume among salt sensitive versus resistant people ²⁷, ²⁸. Instead, salt sensitive individuals lack the vasodilator response to salt that is seen in salt resistant people ²⁷-²⁹. These findings implied that salt sensitive hypertension may be related to pathophysiological mechanisms leading to vascular dysfunction.
The recent shift in our understanding of body Na\(^+\) distribution has major implications for the pathophysiological explanation of salt sensitivity. Previously, salt was thought to be distributed in the intravascular, interstitial and intracellular compartments only isoosmolarly. However, Titze et al. found that Na\(^+\) can be stored in the interstitium of tissue non-osmotically without commensurate water, but instead via glycosaminoglycans\(^{12,13}\). Later, clinical studies of \(^{23}\)Na MRI revealed that Na\(^+\) is stored in the interstitial of skin and skeletal muscle in humans\(^{30}\). The concentration of this stored Na\(^+\) has been correlated with higher blood pressure\(^{30,31}\). While the relationship between tissue Na\(^+\) storage and salt sensitivity is still unknown, differences in the regulation of this storage has been hypothesized to affect salt sensitivity\(^{32,33}\).

The role of inflammation in salt sensitive hypertension

Studies in the last decade have established a strong relationship between inflammation and hypertension\(^{34}\). Individuals with hypertension are characterized by high serum inflammatory markers, including C-reactive protein, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)\(^{35-37}\). Among patients with hypertension, higher levels of inflammatory markers in serum and urine is associated with target organ damage\(^{38}\). Furthermore, prospective studies in non-hypertensive populations found serum inflammatory markers to be significant predictors of de novo development of hypertension\(^{39-41}\), suggesting that inflammation plays a role in the pathogenesis of hypertension.

Studies of experimental hypertension have provided evidence for the causality of this relationship. Earlier studies in 1960s and 1970s found that immunosuppression decreased blood pressure\(^{42}\), while adoptive transfer of lymph node cells from animals with kidney infarction induced hypertension in healthy animals\(^{43}\). Moreover, the thymus was essential for the development of salt sensitive hypertension in animal models\(^{43,44}\). Guzik et al later showed that mice lacking T lymphocytes were protected from hypertension and related vascular dysfunction\(^{45}\). Similarly, studies by Dr. Steven Crowley et al. demonstrated that mice with
severe combined immunodeficiency had a blunted response to hypertensive stimuli. Further studies showed that oligoclonal populations of cytotoxic CD8+ T cells induce hypertension through vascular remodeling in the kidney and Na+ retention. Depletion of T cells or the cytokine IL-17A of T cells attenuated experimental hypertension and related endothelial and renal dysfunction in mice. T cell infiltration in the kidneys and perivascular space due to hypertension is particularly important as a cause of kidney damage and further increase in blood pressure as a result.

Pro-inflammatory cytokines released from APCs and T-cells are also crucial for the development of hypertension. Antagonism of cytokines IL-6, TNF-alpha, and IL-17A lowers blood pressure and attenuates endothelial dysfunction. Further evidence has shown a role of almost every immune cell, of innate and adaptive immunity, in the development of hypertension (Figure 1), and has been discussed in detail elsewhere.

The role of antigen presenting cells in Hypertension

Activation of T lymphocytes occurs via their interaction with professional APCs, implying that APCs would play a significant role in the relationship between immunity and hypertension. Indeed, the necessity of APC activation and co-stimulation in the development of hypertension has been shown by Vinh et al. over a decade ago. Mice lacking B7 ligand (CD80 and CD86) on APCs demonstrated minimal blood pressure response to Ang II as well as vascular inflammation. Similarly, pharmacological blockage B7 ligand (CD80 and CD86) costimulation on APCs by CTLA4-Ig abrogated hypertensive effects of both deoxycorticosterone acetate (DOCA)-salt and ang II. Recent studies by Crowley et al. found that classical DCs promoted T cell activation in the kidney following renin angiotensin system (RAS) activation, leading to oxidative stress and renal fluid retention that resulted in experimental hypertension. The costimulatory ligand CD70 on APCs, which is essential for the formation of memory T cells, was also shown to contribute to increased blood pressure and renal dysfunction in response to mild
hypertensive stimuli. In mice fed with high salt, CD70 expression in APCs increase by up to 5 fold and effector memory T cells proliferate and redistribute to the kidneys, leading to kidney damage and hypertension\textsuperscript{60}.

Recent studies have found significant APC and lymphocyte infiltration of renal interstitium in salt sensitive hypertension\textsuperscript{33, 61, 62}, the degree of which also correlates with the severity of hypertension\textsuperscript{63, 64}. The attenuation of the tubulointerstitial inflammation in the kidneys improves or reverts hypertension\textsuperscript{65, 66, 67}. In rat models of salt sensitive hypertension, immunosuppression with mycophenolate mofetil prevents renal infiltration of monocytes and macrophages and decreases blood pressure. Similarly, APC-mediated inflammation appears to mediate vascular dysfunction in hypertension\textsuperscript{68, 69}. Monocyte and macrophage infiltration in the perivascular space is crucial in the blood pressure effects of ang II in rodents\textsuperscript{68, 69}. The interplay observed between systemic inflammation and vascular stiffness in hypertensive patients\textsuperscript{70-72} may be mediated by perivascular infiltration of these cells. Mice with excess vascular oxidative stress, achieved by overexpression of NADPH oxidase in smooth muscle, develop aortic stiffening and hypertension\textsuperscript{49, 73}. Importantly, the prohypertensive effect of oxidative stress was mediated by the formation of isolevuglandins (IsoLGs) in the vasculature\textsuperscript{73}. IsoLGs are highly reactive products of fatty acid oxidation that activate APCs, and subsequently T cells\textsuperscript{74}. These IsoLG-activated immune cells infiltrate the vascular adventitia, which results in collagen deposition, stiffening and hypertension\textsuperscript{73}.

Endogenous molecules, physiologically identified as “self” can be recognized as neoantigens by APCs following various alterations such as post-translational modification, oxidation or adduct formation. Such modified proteins may serve as potential antigens triggering an immune activation in salt sensitive hypertension. Heat shock protein 70 (HSP70) is one such molecule that has been suggested to drive T cell influx into the kidney. HSP70 expression is increased in lymphocytes isolated from hypertensive humans\textsuperscript{75} and kidneys of hypertensive
animals\textsuperscript{76}. In rat models of salt-induced hypertension, overexpression of HSP70 was found to drive a CD4 clonal response. Immune tolerization of the animals to HSP70 prevents renal inflammation and the development of salt sensitive hypertension. Adoptive transfer of tolerant T cells also corrects hypertension in non-tolerized animals\textsuperscript{77}.

Recently, we have discovered a pathway by which salt-induced formation of neoantigens in APCs mediate an inflammatory response in hypertension, leading to hypertensive end-organ damage. Our findings revealed that Na\textsuperscript{+} entry into APCs triggers a cascade of events that results in the formation of IsoLGs\textsuperscript{7, 14}. As highly reactive oxidative products of arachidonic acid metabolism, IsoLGs adduct to the lysine residues on proteins, giving rise to IsoLG-protein adducts. These IsoLG-protein adducts act as neoantigens and trigger T cell activation, leading to inflammation in salt sensitive hypertension. Importantly, the Na\textsuperscript{+} entry into APCs is mediated by ENaC, implying that ENaC contributes to the regulation of blood pressure through immune mediated mechanisms in addition to its traditional role in renal Na\textsuperscript{+} transport\textsuperscript{7, 14}.

An intricate relationship between APCs, body Na\textsuperscript{+} balance and hypertension has also been suggested in recent studies by Machnik et al. Their results showed that high salt diet leads to increased interstitial Na\textsuperscript{+} accumulation in the skin, which in turn drives hyperplasia of the lymph capillary network and enhanced interstitial Na\textsuperscript{+} clearance. High salt-induced activation of tonicity-responsive enhancer binding protein (TonEBP) in macrophages and DCs trigger the secretion of vascular endothelial growth factor-C (VEGF-C). The tissue infiltration of these APCs and TonEBP-VEGF-C driven response reorganize the lymph capillary system and enhance nitric oxide synthase (eNOS) expression, mitigating the high-salt induced changes in blood pressure\textsuperscript{78, 79}. Blockage of this pathway, either via APC depletion or inhibition of VEGF-C response amplifies interstitial volume retention, decreases eNOS and augments the salt-induced increase in blood pressure\textsuperscript{78}. Further studies by the group demonstrated similar responses by skin APCs to isotonic salt or DOCA-salt treatment in rat models of salt sensitivity.
Lack of this physiological APC regulation of lymphangiogenesis resulted in the development of salt sensitivity from a salt resistant state\textsuperscript{80}.

The classical role of renal ENaC in salt sensitive hypertension

The amiloride-sensitive ENaC has a central role in maintaining the body Na\textsuperscript{+} and water balance, thus blood pressure. ENaC mediated Na\textsuperscript{+} reabsorption in the distal part of renal tubule constitutes the rate-limiting step of transepithelial Na\textsuperscript{+} reabsorption. The activity of ENaC in the kidney is strictly regulated by aldosterone, as well as other hormones involved in the control of blood pressure including arginine vasopressin and atrial natriuretic peptide\textsuperscript{81-83}. Although the role of ENaC and its action in the renal duct to affect Na\textsuperscript{+} homeostasis and blood pressure is well-established\textsuperscript{84, 85} (Figure 2), its role in the development of hypertension outside of the kidneys is still poorly characterized.

In normal physiology, salt or water deprivation triggers renin-angiotensin-aldosterone system and vasopressin secretion, stimulating ENaC and restoring blood pressure. Abnormally high channel function, on the other hand, produces hypertension. ENaC mutations causing constitutively active channel lead to Mendelian forms of hypertension, namely Liddle syndrome; while loss of function mutations of ENaC result in pseudohypoaldosteronism type 1, characterized by severe hypotension and renal salt wasting\textsuperscript{8}. Furthermore, a number of ENaC single nucleotide variants have been identified in humans. These polymorphisms are linked to functional changes in the channel and its overactivation\textsuperscript{86-88} although their effects on the risk of developing hypertension remain unclear\textsuperscript{89}. Notably, pharmacological blockage of ENaC with amiloride has been shown to effectively reduce blood pressure in patients with refractory hypertension\textsuperscript{90, 91} and hypertension resistant to mineralocorticoid antagonism\textsuperscript{92}. 

The role of ENaC in immune activation in salt sensitive hypertension

In addition to the distal nephron, ENaC is expressed in various tissues including the lungs, pancreas, vasculature and nervous system. ENaC is vastly expressed in the vascular smooth muscle of renal, mesenteric and cerebral arteries where its inhibition leads to loss of myogenic response and pressure-induced vasoconstriction. Importantly, the discovery of ENaC expression in the antigen presenting DCs has provided a link between immunity and hypertension through an ENaC-mediated inflammatory response. In high extracellular Na+ concentrations, the entry of Na+ through ENaC triggers calcium (Ca2+) influx into the DC via the Na+/Ca2+ exchanger, which in turn activates protein kinase C (PKC). Phosphorylation of NADPH oxidase by PKC leads to superoxide and IsoLGs formation. The adduction of these highly reactive oxidative products on endogenous proteins gives rise to IsoLG-protein adducts. These immunogenic adducts activate the cell as well as T cells through their presentation on MHC molecules. This ENaC-mediated salt response leads to the production of IL-1β and IL-6 in DCs and the pro-hypertensive cytokines IFN-γ and IL-17A in T cells, promoting the development of hypertension and end-organ damage. Pharmacological scavenging of IsoLGs abrogates the sodium-induced inflammatory response and elevation in blood pressure.

Importantly, the osmotically inactive Na+ accumulation in the interstitium of muscle and skin provide an ideal extracellular environment for salt-induced, ENaC mediated APC activation. Indeed, human studies using Na MRI have showed that the tissue Na+ concentrations in individuals with hypertension are comparable to the levels that would activate DCs. These findings were corroborated by animal studies, showing that a high salt diet leads to similar interstitial Na+ concentrations. The finding that ENaC mediates the entry of Na+ into the APCs imply that ENaC may play a pivotal role in the regulation of blood pressure through immune activation as well as its well-recognized function in the nephron.
Impact of immune cell-derived cytokines on ENaC and other renal Na⁺ transporters

In hypertension, immune cells infiltrate the kidney and release cytokines, a process that has been recently shown to regulate renal sodium excretion. Blood pressure is directly dependent on the activity of renal sodium transporters in the nephron, the activity of which is modulated by pro-hypertensive inflammatory cytokines. Zhang et al found that angiotensin II-induced hypertension was associated with increased activation of the interleukin 1 receptor on resident renal-myeloid cells and enhanced Na-K-Cl cotransporter 2 NKCC2 activity, leading to enhanced sodium reabsorption. On the other hand, blockage of IL-1 receptor prevents the maturation of intra-renal myeloid cells into macrophages that secrete nitric oxide and suppress NKCC2-mediated sodium reabsorption. In addition, we and others have found that IL-17A increases renal sodium–hydrogen exchanger 3 (NHE3) and sodium-chloride cotransporter (NCC) activity through phosphorylation of serum- and glucocorticoid-regulated kinase 1 (SGK-1). A recent study by Veiras et al found that high salt diet-induced hypertension in diabetic mice was associated with increased IL-6 production by CD80⁺ macrophages and ENaC activity. Treatment with anti-IL-6 antibody suppressed the inflammatory response by inhibiting IL-1β release from renal tubular epithelial cells and prevented the development of salt sensitivity, a process regulated by SGK-1 in a sex-specific manner.

Perspectives

Salt sensitivity of blood pressure is a phenotype closely associated with increased cardiovascular risk and renal end-organ damage. It has been over three decades since Weinberger et al. showed that salt sensitivity is a cardiovascular risk factor as strong and yet independent of hypertension. While our understanding of the pathogenesis and etiologies of salt sensitivity has immensely broadened, the exact mechanisms remain to be uncovered. This goal is particularly critical since approximately half of all hypertensive patients are salt sensitive,
setting salt sensitivity as an important target for public health interventions. Unfortunately, we are still far from being able to provide antihypertensive treatment strategies targeted to salt sensitivity. Thus, it is crucial for us to better understand the mechanisms of body Na\(^+\) regulation and how certain populations respond differently to dietary salt.

The immune system has an evident role in salt sensitive hypertension. Our recent findings suggest that immune cell activation by ENaC-regulated Na\(^+\) transport and related oxidative stress in APCs may contribute to hypertension and may provide a therapeutic strategy against its development\(^\text{14}\). While immunomodulatory therapies are currently not in use for hypertension, immunosuppression has been shown to have blood pressure lowering effects in animal and human studies \(^\text{107, 108}\). Furthermore, several commonly prescribed antihypertensives have been suggested to exert these effects through anti-inflammatory and antioxidant actions\(^\text{109}\). It is yet unknown whether these medications can modulate salt-induced APC activation and whether such modulation by other therapies may potentially play a role in the management of salt sensitive patients. Regardless, research should investigate Na\(^+\) accumulation in the tissue and salt induced immune cell activation as potential targets. Once therapies targeting salt-induced inflammation are investigated, additional research would be needed to assess if such therapies would improve cardiovascular outcomes in the salt sensitive population.
Disclosures

A. Kirabo reports the following: Patents or Royalties: Methods for Treating Inflammation and Hypertension with Gamma-Ketoaldehyde Scavengers; U.S. Patent # 14/232,615; and Advisory or Leadership Role: American Heart Association; Associate Editor - Circulation Research, 2019 - present; Hypertension Editorial Board Member, 2018 - present; Section Editor for Inflammation and Cardiovascular Diseases, Current Hypertension Reports, 2018 - present; AJP-Heart and Circulatory Physiology Editorial Board member, 2021 - present; AJP-Heart and Circulatory Physiology Consulting Editor board, 2021 - present. L. Ertuglu has nothing to disclose.

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Author Contributions

Lale Ertuglu: Conceptualization; Writing - original draft; Writing - review and editing. Annet Kirabo: Conceptualization; Supervision; Validation; Writing - original draft; Writing - review and editing.
References


Figure Legends

Figure 1: An overview of the role of immune system in hypertension. The cells of both the innate and adaptive immunity have been shown to play roles in the development of hypertension through the production of pro-inflammatory cytokines. The role of APCs in this paradigm is the main focus of discussion herein.

Figure 2: The renal and extrarenal roles of ENaC in the regulation of blood pressure. ENaC-mediated blood pressure effects in kidney, vasculature and immune system. ENaC is critical in Na⁺ reabsorption in distal renal tubular cells, where its activity is tightly regulated by aldosterone (aldo) and mineralocorticoid receptor (MR). ENaC is also expressed in the smooth muscle cell. ENaC mediated sodium entry leads to increased intracellular calcium (Ca²⁺) and nitric oxide (NO), regulating the vascular tone. Na⁺ entry into the APCs through ENaC activity also leads to intracellular Ca²⁺ entry, which activates protein kinase C (PKC) and subsequently NADPH oxidase. Superoxide production by NADPH oxidase results in the formation of IsoLGs, which adduct to proteins and generate neoantigens that induce immune activation in hypertension.

Figure 3: The proposed relationship between tissue sodium accumulation and immune activation. High salt diet leads to Na⁺ accumulation in skin related to glycosaminoglycans (GAG). ENaC mediated Na⁺ entry into the APCs in such high extracellular Na⁺ concentrations results in production of ROS and IsoLG adducts. IsoLG adducts are immunogenic neoantigens and trigger the secretion of pro-inflammatory cytokines from the APC as well as T cells following their presentation through MHC complex. Resulting inflammatory response and immune cell infiltration causes vascular and renal injury and subsequent salt sensitive hypertension.