CURRENT OPINION

Dendritic cell epithelial sodium channel induced inflammation and salt-sensitive hypertension

Mert Demirci[a], *Antentor Hinton*[b] *and Annet Kirabo*[c,d,e,f]

Purpose of review
Salt sensitivity of blood pressure (SSBP) is an independent risk factor for cardiovascular disease. Epithelial sodium channel (ENaC) plays a critical role in renal electrolyte and volume regulation and has been implicated in the pathogenesis of SSBP. This review describes recent advances regarding the role of ENaC-dependent inflammation in the development of SSBP.

Recent findings
We recently found that sodium enters dendritic cells via ENaC, a process regulated by serum/glucocorticoid-regulated kinase 1 and epoxyeicosatrienoic acid 14,15. Sodium entry activates NADPH oxidase, leading to the production of isolevuglandins (IsoLGs). IsoLGs adduct self-proteins to form neoantigens in dendritic cells that activate T cells and result in the release of cytokines promoting sodium retention, kidney damage, and endothelial dysfunction in SSBP. Additionally, we described a novel mechanistic pathway involving ENaC and IsoLG-dependent NLRP3 inflammasome activation. These findings hold promise for the development of novel diagnostic biomarkers and therapeutic options for SSBP.

Summary
The exact mechanisms underlying SSBP remain elusive. Recent advances in understanding the extrarenal role of ENaC have opened a new perspective, and further research efforts should focus on understanding the link between ENaC, inflammation, and SSBP.

Keywords
epithelial sodium channel, hypertension, immune activation, inflammation, salt sensitivity

INTRODUCTION

High salt consumption is a well established cause of hypertension [1], yet blood pressure responses to changes in sodium and extracellular fluid balance vary widely in humans [2]. Salt sensitivity of blood pressure (SSBP) is defined as the heterogeneity in blood pressure responses to dietary salt intake. Approximately 25% of normotensive and 50% of hypertensive people have SSBP [3], which is an independent risk factor for cardiovascular mortality [4]. Previous studies mainly focused on the vasculature, kidneys, and sympathetic nervous system when investigating the mechanisms of SSBP, whereas more recent data suggest that cells of the immune system can sense sodium, although the exact mechanisms remain unclear.

The epithelial sodium channel (ENaC) has a well known role in sodium regulation in the kidneys, indirectly influencing blood pressure. Evidence also suggests that ENaC can modulate blood pressure via kidney-independent mechanisms. Our group previously showed that ENaC-regulated sodium transport in antigen-presenting cells (APCs) leads to oxidative stress and immune system activation [5,6]. In this review, we discuss the current understanding of how ENaC contributes to systemic and local inflammation, particularly the role of dendritic cells in salt-sensitive hypertension.

[a]Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, [b]Department of Molecular Physiology and Biophysics, Vanderbilt University, [c]Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical Center, [d]Vanderbilt Center for Immunobiology, [e]Vanderbilt Institute for Infection, Immunology and Inflammation and [f]Vanderbilt Institute for Global Health, Nashville, Tennessee, USA

Correspondence to Annet Kirabo, DVM, MSc, PhD, FAHA, Vanderbilt University Medical Center, Room 536 Robinson Research Building, Nashville, TN 37232-6602, USA. Tel: +1 615 343 0933; e-mail: Annet.Kirabo@vumc.org

Curr Opin Nephrol Hypertens 2024, 33:145–153

DOI:10.1097/MNH.0000000000000963

KEY POINTS

- SSBP is a phenotype that refers to an individual's blood pressure response to changes in dietary salt intake, is an independent risk factor for cardiovascular morbidity and mortality, and it is observed in 25% of normotensive and 50% of hypertensive populations.
- Recent advancements in understanding the regulation and distribution of various subtypes of ENaC in humans have unveiled potential diagnostic biomarkers and therapeutic options for SSBP.
- Since the exact mechanisms underlying SSBP remain elusive, future studies must be directed towards determining the underlying mechanisms of ENaC-induced inflammation in SSBP.

INFLAMMATION AND SALT-SENSITIVE HYPERTENSION

Inflammation is a vital biological reaction triggered by disruptions in tissue homeostasis, such as tissue injury or infection. It plays a crucial role in restoring homeostasis, acts as a host defence mechanism against infectious agents, and facilitates tissue repair [7]. Multiple components, such as extracellular matrix, inflammatory cytokines, and cell surfaces, collectively initiate and mediate the inflammatory response. However, inflammation can become detrimental when it is uncontrolled or sustained. More than five decades of research have confirmed the important role of inflammation in the development and progression of hypertension. A meta-analysis of prospective and retrospective cohort studies demonstrated that elevated inflammatory markers, including C-reactive protein, interleukin (IL)-6, and tumour necrosis factor-alpha (TNF-α), are associated with an increased risk of developing hypertension [8].

APCs, including macrophages, dendritic cells, and B cells, are essential for initiating the inflammatory response to hypertensive stimuli. After their identification by Steinman *et al.* [9] in 1973, dendritic cells have been postulated as the most potent APC. APCs interact with T cells via major histocompatibility complex interactions and express co-stimulatory molecules after activation [10]. Initial evidence of the connection between the immune system and hypertension was obtained from animal models of hypertension demonstrating the blood pressure–lowering effects of immunosuppression [11]. Earlier studies also described inflammatory cell infiltration in the vasculature of humans with hypertension of various aetiologies [12]. Subsequent animal studies revealed that thymus transplantation in spontaneously hypertensive rats led to suppression of hypertension by restoring the immune system [13]. Guzik *et al.* [14] showed that T cell transplantation restored the attenuated hypertensive response to angiotensin II infusion in immunodeficient RAG1-/- mice, emphasizing the crucial role of T cells in the development of hypertension and vascular dysfunction. Crowley *et al.* [15] corroborated these results by demonstrating that immunodeficient mice are resistant to developing hypertension following chronic angiotensin II infusion and exhibit less myocardial hypertrophy and kidney injury, compared to wild-type control animals.

In animal models of hypertension, high dietary salt promotes infiltration of APCs and T cells into the kidneys [16▪], resulting in tissue damage and local inflammation through the secretion of cytokines, such as IL-17, TNF-α, and interferon-gamma (IFN-γ) [6]. IFN-γ blockade reduces cardiac damage without affecting blood pressure in angiotensin II induced hypertensive murine models, suggesting that targeting inflammatory pathways may benefit patients with hypertension by reducing cardiovascular damage, independent of blood pressure control [17]. Recent studies have provided a more comprehensive understanding of the relationship between the immune system and hypertension, as described below.

PATHOPHYSIOLOGY OF SALT-SENSITIVE HYPERTENSION

In Arthur Guyton's classical hypothesis, increased sodium intake leads to an increase in plasma volume and subsequent increase in blood pressure [18]. In compensation, renal sodium handling mechanisms attempt to restore blood pressure to normal levels [19]. Based on these assumptions, impaired renal sodium handling was considered the main factor behind salt-sensitive hypertension. According to this hypothesis, salt-sensitive individuals require a higher blood pressure to excrete the same amount of sodium as salt-resistant patients, and a certain level of dysfunctional natriuresis is necessary to initiate the sequence of events resulting in hypertension. While the exact pathophysiology of SSBP remains controversial, the old theory of variability in cardiac output to maintain adequate natriuresis is insufficient to explain the variance in SSBP. Fernando Elijovich and colleagues at Vanderbilt University showed that cardiac output and renal sodium handling do not differ significantly between salt-sensitive and salt-resistant individuals [20]. Accordingly, disturbances in multiple systems, including the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), and gastrointestinal system, have been postulated to be involved in salt-sensitive hypertension [21–23].

Recent discoveries regarding sodium distribution in the body have greatly advanced our understanding of the physiologic factors potentially contributing to SSBP. Traditionally, sodium was thought to be equally distributed among the intravascular, interstitial, and intracellular compartments, as sodium is the key factor controlling blood volume and osmolarity. However, Titze *et al.* [24] demonstrated that the skin interstitium has the capacity to store substantial amounts of sodium without causing water retention. In other words, sodium accumulates nonosmotically in skin and cartilage tissue, which is considered an extracellular compartment that is not regulated solely by the kidney's sodium handling mechanisms [24,25]. Several cross-sectional studies showed that tissue sodium storage is increased in patients with hypertension, and the amount of storage correlates with blood pressure measurements and urinary sodium excretion, in addition to varying with age and sex [26,27]. However, a pilot randomized clinical trial demonstrated that sodium content in the skin or muscle tissues of patients with hypertension did not decrease following 8 weeks of dietary salt restriction or diuretic interventions, and chlorthalidone intervention paradoxically increased muscle sodium content [28]. This increase may reflect storage of sodium in tissues as a compensatory mechanism for decreased blood sodium [28].

Vascular dysfunction was also postulated to contribute significantly to SSBP in humans [20], and subsequent animal experiments confirmed this by demonstrating a lack of vasodilatory response to salt loading in salt-sensitive rats [29]. Seminal discoveries regarding the interrelationship between T cell infiltration and vascular dysfunction led us to hypothesize that immune cell activation may cause vascular dysfunction, ultimately contributing to the development of salt-sensitive hypertension.

ROLE OF EPITHELIAL SODIUM CHANNEL IN HUMAN TISSUES

Strict control of sodium transport in kidneys is fundamental for fluid and electrolyte homeostasis. Amiloride-sensitive ENaC is responsible for facilitating sodium ion entry through the apical side of principal cells, and its role in sodium handling has been extensively studied. This function is crucial, as it is the rate-limiting step for transporting sodium ions across principal cells in aldosterone-sensitive distal portions of the nephron. Activity and surface expression of ENaC are regulated by various hormonal signals, such as arginine vasopressin; serum/glucocorticoid regulated kinase 1 (SGK1) [30,31], through the influence of aldosterone [32]; and nonhormonal signals, such as basolateral levels of potassium [33,34,35], epoxyeicosatrienoic acids (EETs) [36], and extracellular sodium itself [37] (Fig. 1). Moreover, elevated intracellular sodium and osmolarity trigger degradation of ENaC as a self-inhibitory mechanism [38]. These regulatory mechanisms are crucial for maintaining sodium levels according to the body's physiologic needs. Diminished ENaC function results in severe complications, such as excessive loss of sodium and retention of potassium ions, leading to disruptions in electrolyte balance. Conversely, increases in ENaC activity could potentially contribute to the development of essential hypertension.

ENaC is a sodium-selective channel composed of four distinct subunits, α, β, γ, and δ— encoded by the sodium channel 1 subunit alpha (*SCNN1A)*, *SCNN1B*, *SCNN1G*, and *SCNN1D* genes, respectively [39]. These subunits display varying patterns of tissue expression, suggesting variability in their functional and regulatory properties in different tissues (Fig. 2). Following cloning of the α, β, and γ subunits [40], the fourth subunit (δ) was discovered in human tissues [41]. Notably, δ-ENaC is not expressed in commonly studied rodent models, which limits research on this subunit [42]. The δ subunit shares notable amino acid sequence similarities with the α subunit and can create channels with β and γ subunits or independently. These subunits combine to form ENaC, primarily as αβγ (α-ENaC) or δβγ (δ-ENaC) heterotrimers [31,41]. Importantly, δ-ENaC differs from α-ENaC in terms of its body location and channel characteristics [43], as discussed in detail elsewhere [39]. δ-ENaC is not only significantly expressed in tissues not primarily associated with sodium reabsorption (e.g., lungs, cerebral cortex, hypothalamus, pituitary gland) [44], but it is also expressed in APCs [31,45▪▪] (Fig. 2). Despite relatively low δ-ENaC expression in human kidneys, we found a correlation between *SCNN1D* variants and blood pressure [31], suggesting that extrarenal sodium handling by ENaC plays a role in blood pressure regulation.

ENaC is also expressed in lingual epithelium and facilitates salt tasting, which may influence sodium intake [46]. In the colon, it facilitates sodium absorption [47]. Moreover, ENaC in vascular endothelial [48] and smooth muscle cells can serve as a mechanosensor, potentially controlling peripheral vascular resistance through shear force–sensing mechanisms [49,50], and enhanced ENaC activity at these locations contributes to vascular dysfunction in many diseases [51,52] (Fig. 2).

Various ENaC gene mutations have been identified in individuals with inherited forms of hypertension and hypokalaemia, known as Liddle syndrome (described by Grant Liddle at Vanderbilt University).

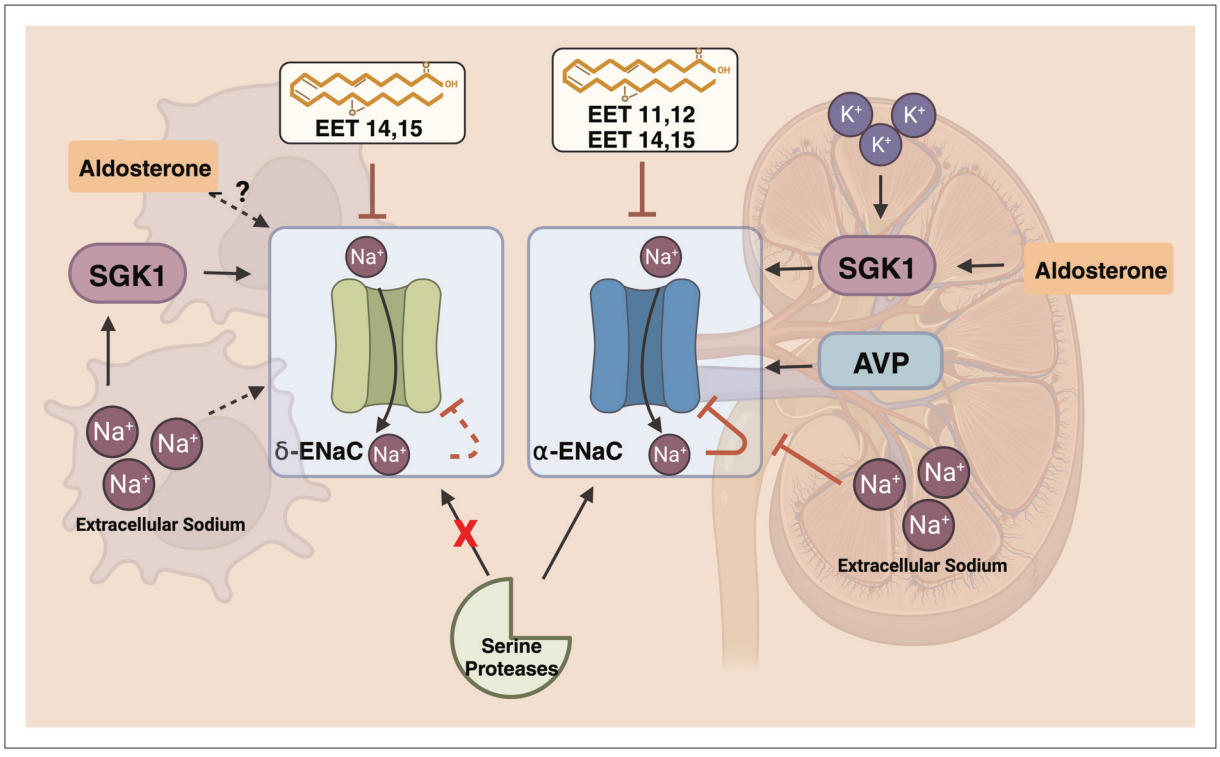

FIGURE 1. Regulation of αβγ and δβγ epithelial sodium channels. α-ENaC (αβγ) is the predominant ENaC in the kidneys and can be downregulated by both extracellular and intracellular sodium levels. By contrast, δ-ENaC (δβγ) is insensitive to sodium self-inhibition, and extracellular sodium entry activates serum/glucocorticoid–regulated kinase 1 (SGK1) in immune cells. Membrane-bound serine proteases activate α-ENaC, whereas δ-ENaC is insensitive to proteases. AVP, arginine vasopressin; EET, epoxyeicosatrienoic acid.

These mutations disrupt interactions between the ENaC β or γ-subunit and ubiquitin ligase, resulting in increased channel expression at the plasma membrane and increased probability of channel opening [53]. Conversely, loss-of-function mutations in α, β, and γ genes lead to pseudo-hypoaldosteronism type 1, characterized by hypotension and hyperkalaemia [54]. These findings emphasize the crucial role of ENaC in regulating blood pressure, as well as potassium homeostasis [33].

ROLE OF EPITHELIAL SODIUM CHANNEL IN IMMUNE ACTIVATION IN SALT-SENSITIVE HYPERTENSION

Our research group has made significant discoveries regarding the role of salt-induced neoantigens in APCs and their effects on inflammation and hypertensive end-organ damage [6]. The initiating step is sodium influx into APCs via ENaC [5] (Fig. 3). We discovered that under conditions of high extracellular sodium, assembly of ENaC subunits is promoted by the salt-sensing kinase SGK1 in APCs [55]. This assembly facilitates entry of sodium into APCs through ENaC and initiates a series of reactions that generate highly reactive oxidative products called isolevuglandins (IsoLGs), which are products of arachidonic acid metabolism [6] and react with lysine residues on endogenous proteins to form IsoLG-protein adducts that accumulate in APCs. These adducts are presented to T cells as neoantigens, triggering the synthesis of IL-6, IL-1β, and IL-23, which stimulate the differentiation of naive T cells into pro-inflammatory T cells, particularly T helper 17 cells that produce IL-17A [56]. Consequently, IsoLG-activated immune cells infiltrate vascular adventitia and the kidneys, secreting IL-17A, IL-21, TNF-α, and IFN-γ [57]. We demonstrated that the kidney corticomedullary junction, where interstitial sodium levels can exceed 1000 mOsM, serves as a crucial site for APC activation [16▪]. Overall, this activation cascade results in inflammation, vascular dysfunction, and eventual fibrosis and hypertension [58]. Indeed, scavenging IsoLG adducts by treatment with 2-hydroxybenzylamine attenuated these complications in murine models [58].

REGULATION OF IMMUNE CELL EPITHELIAL SODIUM CHANNEL

The basis for differences in ENaC-dependent IsoLG formation between individuals with salt-sensitive

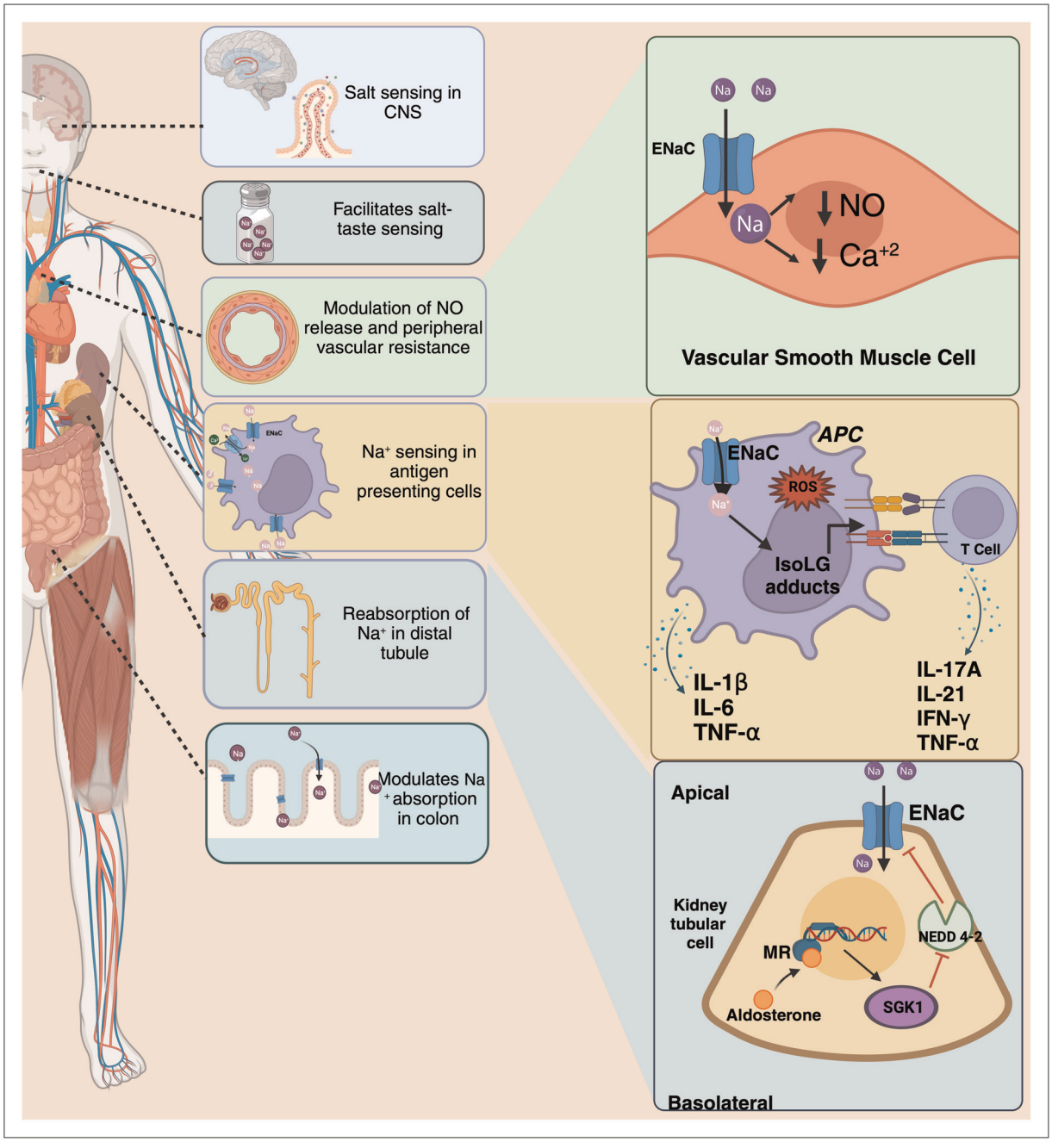

FIGURE 2. Renal and extrarenal roles of epithelial sodium channels in human tissues. APC, antigen-presenting cell; CNS, central nervous system; eNOS, endothelial nitric oxide synthase; IFN-γ, interferon-gamma; IL, interleukin; IsoLG, isolevuglandins; MR, mineralocorticoid receptor; NEDD 4-2, neural precursor cell-expressed developmentally downregulated 4 ligase; NO, nitric oxide; ROS, reactive oxygen species; SGK1, serum/glucocorticoid regulated kinase 1; TNF-α, tumour necrosis factor-alpha.

versus salt-resistant hypertension remains controversial, as the level of IsoLG production in APCs varies considerably. EETs are arachidonic acid pathway metabolites that have been postulated to regulate salt sensitivity through ENaC inhibition [36,59]. In a series of experiments, we demonstrated that EETs regulate IsoLG adduct production in APCs. Specifically, urinary levels of EET 14,15 (one of the most common EET regioisomers) were negatively correlated with changes in IsoLGs in monocytes, and baseline IsoLG levels were directly correlated with salt-sensitivity index in patients with hypertension [45▪▪]. These data suggest that IsoLG and urinary EET 14,15 levels may be potential biomarkers for diagnosing SSBP.

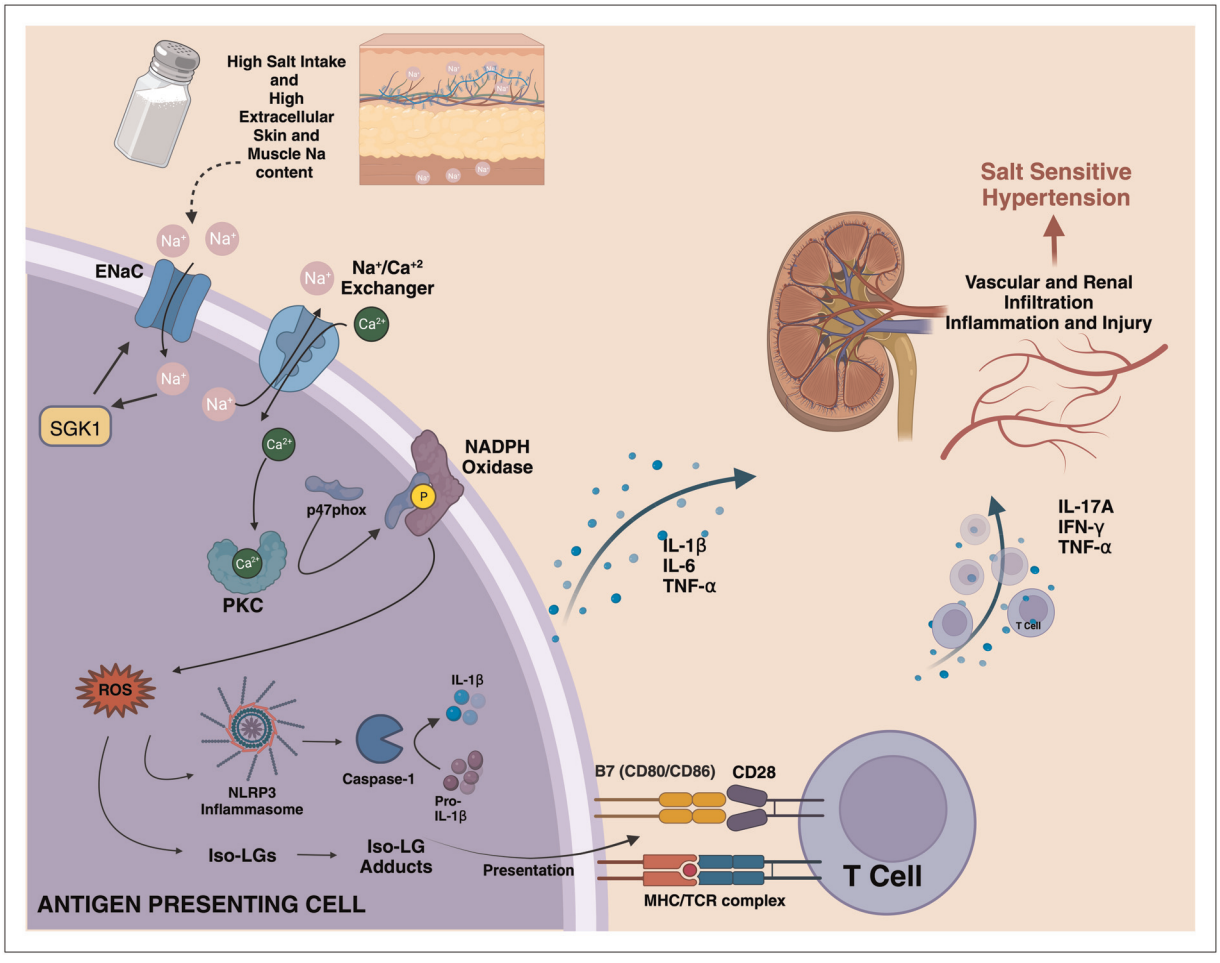

FIGURE 3. Overview of the role of the interaction between antigen-presenting cells and T cells in salt-sensitive hypertension. ENaC-dependent sodium transport in APCs triggers the Na^{+}–Ca^{2+} exchanger. The resulting increase in intracellular calcium activates protein kinase C (PKC), which subsequently phosphorylates p47phox and activates NADPH oxidase. This leads to the generation of reactive oxygen species (ROS) and isolevuglandins (IsoLGs). NLRP3, NOD-like receptor family pyrin domain containing 3; P, phosphate; TCR, T cell receptor; IL, interleukin; TNF-α, tumour necrosis factor-alpha; IFN-γ, interferon-gamma.

RAAS is a critical regulator of blood pressure, and various components of the RAAS signalling pathway can directly impact immune cell function [60]. We recently investigated in-vitro expression of RAAS-related genes in human monocytes from healthy individuals in response to high sodium and found that expression of these genes did not correlate with salt-induced activation of myeloid immune cells in salt-sensitive hypertension [61]. These results suggest that RAAS may not play a significant role in regulating immune cell ENaC in SSBP.

DOWNSTREAM SIGNALLING IN EPITHELIAL SODIUM CHANNEL ACTIVATED IMMUNE CELLS

Inflammasome activation is another recent discovery involved in the relationship between inflammation, autoimmunity, and SSBP [62]. Our group recently elucidated the role of NOD-like receptor family pyrin domain containing 3 (NLRP3) in SSBP [62,63▪▪] (Fig. 3). NLRP3 inflammasome is a well characterized mediator of inflammation in several chronic inflammatory diseases, including gout, Crohn's disease [64], and rheumatoid arthritis [65]. It serves as a primary source of circulating IL-1β, a biomarker elevated in atherosclerosis and hypertension [66]. Mice lacking inflammasome or IL-1β components are resistant to developing atherosclerosis [67]. We further demonstrated that dietary magnesium deficiency in mouse models is associated with activation of NLRP3 inflammasome and formation of IsoLG in APCs, resulting in elevated blood pressure in the absence of any alterations in body fluid composition [68]. This finding highlights the potential roles of electrolytes other than sodium in inflammation and SSBP.

TARGETING EPITHELIAL SODIUM CHANNEL IN SPECIFIC PATIENT GROUPS

As discussed above, ENaC is an amiloride-sensitive channel expressed in various human tissues. This prompts us to ask why amiloride is not used as a therapeutic strategy for chronic inflammation resulting from ENaC-dependent immune activation. Although amiloride is effective in patients with refractory hypertension [69], its effects on the immune system remain relatively understudied. Nevertheless, a meta-analysis by John Oates and colleagues at Vanderbilt revealed that treatment with an ENaC inhibitor and thiazide diuretic reduces sudden cardiac death in elderly patients with hypertension. Despite its weak diuretic and antihypertensive effects, use of amiloride to target ENaC-dependent immune activation could be beneficial in certain patient groups.

HIV infection is a well studied immune system disorder. Vascular dysfunction and hypertension are common in people with HIV (PWH) and have been the focus of recent research [70,71]. While various factors contribute to cardiovascular disease in PWH, the relationship between HIV and salt sensitivity has emerged as an intriguing topic. Of note, almost all PWH with hypertension have salt sensitivity [46]. Although the effects of HIV on ENaC are not well understood, we recently showed that SSBP is more prominent in PWH [72], and hypothesized that ENaC contributes to vascular dysfunction in this patient population [73▪]. Novel therapeutic targets specific for ENaC of immune cells may ameliorate vascular dysfunction in PWH.

CONCLUSION

Substantial evidence indicates that sodium can be stored nonosmotically in human tissues and trigger immune system activation. However, the exact mechanisms linking salt-sensitive hypertension and the immune system remain unclear. The landmark discoveries of ENaC in immune cells and subsequent mechanistic pathways leading to IsoLG-mediated immune activation have opened new perspectives in our understanding of the cause of hypertension, yet many questions remain. Blood pressure management continues to be challenging, even for patients highly adherent to their antihypertensive treatments. This may be because existing treatments do not adequately target all mechanisms contributing to hypertension, such as immune activation and tissue sodium accumulation. Further research is required to explore the therapeutic potential of targeting specific inflammatory pathways in SSBP.

Acknowledgements

All figures were originally created using BioRender.com.

Financial support and sponsorship

This study was supported by the National Institutes of Health grants R01HL147818 and R01HL144941 (A.K.).

UNCF/Bristol-Myers Squibb E.E. Just Faculty Fund; the Career Award at the Scientific Interface from the Burroughs Welcome Fund (BWF) (ID #1021868.01); a BWF Ad-hoc Award; a National Institutes of Health (NIH) Small Research Pilot Subaward (5R25HL106365-12) from the NIH PRIDE Program; the Vanderbilt Diabetes and Research Training Center (DK020593); a Chan Zuckerberg Initiative (CZI) Science Diversity Leadership grant (#2022-253529) from the CZI donor-advised fund of Silicon Valley Community Foundation (A.H.).

Conflicts of interest

Kirabo reports US patent #14/232,615 (Methods for Treating Inflammation and Hypertension with Gamma-Ketoaldehyde Scavengers) and an advisory or leadership role for the American Heart Association, Circulation Research (associate editor 2019–present), Hypertension (editorial board member 2018–present), Inflammation and Cardiovascular Diseases (section editor), Current Hypertension Reports (2018–present), AJP-Heart and Circulatory Physiology (editorial board member 2021–present), and AJP-Heart and Circulatory Physiology (consulting editor board 2021–present). The remaining authors have nothing to disclose.

Hinton serves on the following editorial boards: Circulation Research (2022-Present), Aging Cell (2023), American Journal of Physiology- Heart and Circulatory Physiology (2023), Journal of Cell Physiology (2023), Advanced Biology (2022-Present), an Frontiers in Physiology (2023).

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Strazzullo P, D'Elia L, Kandala N-B, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ 2009; 339:b4567.
2. 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 1978; 64:193–198.
3. Weinberger MH, Miller JZ, Luft FC, *et al.* Definitions and characteristics of sodium sensitivity and blood pressure resistance. Hypertension 1986; 8: II127.
4. Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. Hypertension 2001; 37:429–432.
5. Barbaro NR, Foss JD, Kryshtal DO, *et al.* Dendritic cell amiloride-sensitive channels mediate sodium-induced inflammation and hypertension. Cell Rep 2017; 21:1009–1020.
6. Kirabo A, Fontana V, de Faria AP, *et al.* DC isoketal-modified proteins activate T cells and promote hypertension. J Clin Invest 2014; 124:4642–4656.
7. Medzhitov R. Origin and physiological roles of inflammation. Nature 2008; 454:428–435.
8. Jayedi A, Rahimi K, Bautista LE, *et al.* Inflammation markers and risk of developing hypertension: a meta-analysis of cohort studies. Heart 2019; 105:686–692.

9. Steinman RM, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice: I. Morphology, quantitation, tissue distribution. J Exp Med 1973; 137:1142–1162.
10. Kambayashi T, Laufer TM. Atypical MHC class II-expressing antigen-presenting cells: can anything replace a dendritic cell? Nat Rev Immunol 2014; 14:719–730.
11. White F, Grollman A. Autoimmune factors associated with infarction of the kidney. Nephron 1964; 1:93–102.
12. Olsen F. Inflammatory cellular reaction in hypertensive vascular disease in man. Acta Pathol Microbiol Scand A Pathol 1972; 80:253–256.
13. Takeichi N, Suzuki K, Okayasu T, Kobayashi H. Immunological depression in spontaneously hypertensive rats. Clin Exp Immunol 1980; 40:120–126.
14. Guzik TJ, Hoch NE, Brown KA, *et al.* Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. J Exp Med 2007; 204:2449–2460.
15. Crowley SD, Song YS, Lin EE, *et al.* Lymphocyte responses exacerbate angiotensin II-dependent hypertension. Am J Physiol Regul Integr Comp Physiol 2010; 298:R1089–R1097.
16. ▪ Ruggeri Barbaro N, Van Beusecum J, Xiao L, *et al.* Sodium activates human monocytes via the NADPH oxidase and isolevuglandin formation. Cardiovasc Res 2021; 117:1358–1371.

This study showed the correlation between skin sodium levels, monocyte surface activation markers, and intracellular levels of IsoLG adducts.

17. Markó L, Kvakan H, Park J-K, *et al.* Interferon-γ signaling inhibition ameliorates angiotensin II–induced cardiac damage. Hypertension 2012; 60:1430–1436.
18. Guyton AC. Blood pressure control: special role of the kidneys and body fluids. Science 1991; 252:1813–1816.
19. Guyton AC. Kidneys and fluids in pressure regulation. Small volume but large pressure changes. Hypertension 1992; 19(1 Suppl):I2-I8.
20. Laffer CL, Scott RC III, Titze JM, *et al.* Hemodynamics and salt-and-water balance link sodium storage and vascular dysfunction in salt-sensitive subjects. Hypertension 2016; 68:195–203.
21. Drenjančević-Perić I, Jelaković B, Lombard JH, *et al.* High-salt diet and hypertension: focus on the renin-angiotensin system. Kidney Blood Press Res 2011; 34:1–11.
22. Mattson DL, Dasinger JH, Abais-Battad JM. Gut-immune-kidney axis: influence of dietary protein in salt-sensitive hypertension. Hypertension 2022; 79:2397–2408.
23. Ferguson JF, Aden LA, Barbaro NR, *et al.* High dietary salt-induced dendritic cell activation underlies microbial dysbiosis-associated hypertension. JCI Insight 2019; 4:e126241.
24. Titze J, Shakibaei M, Schafflhuber M, *et al.* Glycosaminoglycan polymerization may enable osmotically inactive Na+ storage in the skin. Am J Physiol Heart Circ Physiol 2004; 287:H203–H208.
25. Thowsen IM, Karlsen TV, Nikpey E, *et al.* Na(+) is shifted from the extracellular to the intracellular compartment and is not inactivated by glycosaminoglycans during high salt conditions in rats. J Physiol 2022; 600:2293–2309.
26. Kopp C, Linz P, Dahlmann A, *et al.* 23Na magnetic resonance imaging-determined tissue sodium in healthy subjects and hypertensive patients. Hypertension 2013; 61:635–640.
27. Sahinoz M, Elijovich F, Laffer C, *et al.* Reduction in monocyte isolevuglandins associated with high interstitial sodium mirrors salt-sensitivity of blood pressure in patients with essential hypertension. FASEB J 2021; 35:.
28. Alsouqi A, Deger SM, Sahinoz M, *et al.* Tissue sodium in patients with early stage hypertension: a randomized controlled trial. J Am Heart Assoc 2022; 11:e022723.
29. Potter JC, Whiles SA, Miles CB, *et al.* Salt-sensitive hypertension, renal injury, and renal vasodysfunction associated with Dahl salt-sensitive rats are abolished in Consomic SS.BN1 rats. J Am Heart Assoc 2021; 10: e020261.
30. Lang F, Pearce D. Regulation of the epithelial Na+ channel by the mTORC2/SGK1 pathway. Nephrol Dial Transplant 2016; 31:200–205.
31. Blobner BM, Kirabo A, Kashlan OB, *et al.* Rare variants in genes encoding subunits of the epithelial Na(+) channel are associated with blood pressure and kidney function. Hypertension 2022; 79:2573–2582.
32. Mironova E, Chen Y, Pao AC, *et al.* Activation of ENaC by AVP contributes to the urinary concentrating mechanism and dilution of plasma. Am J Physiol Renal Physiol 2015; 308:F237–F243.
33. McDonough AA, Fenton RA. Potassium homeostasis: sensors, mediators, and targets. Pflugers Arch 2022; 474:853–867.
34. Kortenoeven MLA, Esteva-Font C, Dimke H, *et al.* High dietary potassium causes ubiquitin-dependent degradation of the kidney sodium-chloride cotransporter. J Biol Chem 2021; 297:100915.
35. Sørensen MV, Saha B, Jensen IS, *et al.* Potassium acts through mTOR to regulate its own secretion. JCI Insight 2019; 4:e126910.
36. Pavlov TS, Ilatovskaya DV, Levchenko V, *et al.* Effects of cytochrome P-450 metabolites of arachidonic acid on the epithelial sodium channel (ENaC). Am J Physiol Renal Physiol 2011; 301:F672–F681.
37. Lawong RY, May F, Etang EC, *et al.* Recording sodium self-inhibition of epithelial sodium channels using automated electrophysiology in Xenopus oocytes. Membranes (Basel) 2013; 13:529.
38. Persaud A, Jiang C, Liu Z, *et al.* Elevated intracellular Na(+) and osmolarity stimulate catalytic activity of the ubiquitin ligase Nedd4-2. Proc Natl Acad Sci U S A 2022; 119:e2122495119.
39. Kleyman TR, Eaton DC. Regulating ENaC's gate. Am J Physiol Cell Physiol 2020; 318:C150–C162.
40. Noreng S, Bharadwaj A, Posert R, *et al.* Structure of the human epithelial sodium channel by cryo-electron microscopy. Elife 2018; 7:e39340.
41. Waldmann R, Champigny G, Bassilana F, *et al.* Molecular cloning and functional expression of a novel amiloride-sensitive Na+ channel. J Biol Chem 1995; 270:27411–27414.
42. Ahmad T, Ertuglu LA, Masenga SK, *et al.* The epithelial sodium channel in inflammation and blood pressure modulation. Front Cardiovasc Med 2023; 10:1130148.
43. Ji H-L, Su X-F, Kedar S, *et al.* δ-subunit confers novel biophysical features to αβγ-human epithelial sodium channel (ENaC) via a physical interaction. J Biol Chem 2006; 281:8233–8241.
44. Hanukoglu I, Hanukoglu A. Epithelial sodium channel (ENaC) family: phylogeny, structure-function, tissue distribution, and associated inherited diseases. Gene 2016; 579:95–132.
45. ▪▪ Ertuglu LA, Mutchler AP, Jamison S, *et al.* Eicosanoid-regulated myeloid ENaC and isolevuglandin formation in human salt-sensitive hypertension. Hypertension 2023; 0:.

This article demonstrates the correlation between urinary eicosanoids and salt sensitivity index.

46. Masenga SK, Pilic L, Kirabo A. Salt taste and salt sensitive hypertension in HIV. Curr Hypertens Rep 2023; 25:25–33.
47. Malsure S, Wang Q, Charles RP, *et al.* Colon-specific deletion of epithelial sodium channel causes sodium loss and aldosterone resistance. J Am Soc Nephrol 2014; 25:1453–1464.
48. Ashley Z, Mugloo S, McDonald FJ, Fronius M. Epithelial Na+ channel differentially contributes to shear stress-mediated vascular responsiveness in carotid and mesenteric arteries from mice. Am J Physiol Heart Circ Physiol 2018; 314:H1022–H1032.
49. Fronius M. Epithelial Na+ channel and the glycocalyx: a sweet and salty relationship for arterial shear stress sensing. Curr Opin Nephrol Hypertens 2022; 31:142–150.
50. Paudel P, McDonald FJ, Fronius M. The δ subunit of epithelial sodium channel in humans: a potential player in vascular physiology. Am J Physiol Heart Circ Physiol 2021; 320:H487–H493.
51. Jia G, Habibi J, Aroor AR, *et al.* Epithelial sodium channel in aldosterone-induced endothelium stiffness and aortic dysfunction. Hypertension 2018; 72:731–738.
52. Warnock DG, Kusche-Vihrog K, Tarjus A, *et al.* Blood pressure and amiloride-sensitive sodium channels in vascular and renal cells. Nat Rev Nephrol 2014; 10:146–157.
53. Lemmens-Gruber R, Tzotzos S. The epithelial sodium channel: an underestimated drug target. Int J Mol Sci 2023; 24:7775.
54. Schild L. The ENaC channel as the primary determinant of two human diseases: Liddle syndrome and pseudohypoaldosteronism. Nephrologie 1996; 17:395–400.
55. Van Beusecum JP, Barbaro NR, McDowell Z, *et al.* High salt activates CD11c (+) antigen-presenting cells via SGK (serum glucocorticoid kinase) 1 to promote renal inflammation and salt-sensitive hypertension. Hypertension 2019; 74:555–563.
56. Madhur MS, Lob HE, McCann LA, *et al.* Interleukin 17 promotes angiotensin II–induced hypertension and vascular dysfunction. Hypertension 2010; 55:500–507.
57. Zhang J, Patel MB, Griffiths R, *et al.* Tumor necrosis factor-α produced in the kidney contributes to angiotensin II–dependent hypertension. Hypertension 2014; 64:1275–1281.
58. Wu J, Saleh MA, Kirabo A, *et al.* Immune activation caused by vascular oxidation promotes fibrosis and hypertension. J Clin Invest 2016; 126:50–67.
59. Pidkovka N, Rao R, Mei S, *et al.* Epoxyeicosatrienoic acids (EETs) regulate epithelial sodium channel activity by extracellular signal-regulated kinase 1/2 (ERK1/2)-mediated phosphorylation. J Biol Chem 2013; 288:5223–5231.
60. Ferreira NS, Tostes RC, Paradis P, Schiffrin EL. Aldosterone, inflammation, immune system, and hypertension. Am J Hypertens 2021; 34:15–27.
61. Ertuglu LA, Pitzer Mutchler A, Elijovich F, *et al.* Regulation of human salt-sensitivite hypertension by myeloid cell renin-angiotensin-aldosterone system. Front Physiol 2023; 14:1208270.
62. Ertuglu LA, Mutchler AP, Yu J, Kirabo A. Inflammation and oxidative stress in salt sensitive hypertension; the role of the NLRP3 inflammasome. Front Physiol 2022; 13:1096296.
63. ▪▪ Pitzer A, Elijovich F, Laffer CL, *et al.* DC ENaC-dependent inflammasome activation contributes to salt-sensitive hypertension. Circ Res 2022; 131:328–344.

This article demonstrated the activation of the NLRP3 inflammasome through ENaC-dependent entry of sodium in APCs, which is a novel pathway that potentially contributes to inflammation in SSBP.

64. Schoultz I, Verma D, Halfvarsson J, *et al.* Combined polymorphisms in genes encoding the inflammasome components NALP3 and CARD8 confer susceptibility to Crohn's disease in Swedish men. Am J Gastroenterol 2009; 104:1180–1188.

65. Kim S-K. The mechanism of the NLRP3 inflammasome activation and pathogenic implication in the pathogenesis of gout. J Rheum Dis 2022; 29:140–153.
66. Duewell P, Kono H, Rayner KJ, *et al.* NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 2010; 464:1357–1361.
67. Kirii H, Niwa T, Yamada Y, *et al.* Lack of interleukin-1β decreases the severity of atherosclerosis in ApoE-deficient mice. Arterioscler Thromb Vasc Biol 2003; 23:656–660.
68. Pitzer Mutchler A, Huynh L, Patel R, *et al.* The role of dietary magnesium deficiency in inflammatory hypertension. Front Physiol 2023; 14:1167904.
69. Carter AR, Zhou ZH, Calhoun DA, Bubien JK. Hyperactive ENaC identifies hypertensive individuals amenable to amiloride therapy. Bethesda, MD: American Physiological Society; 2001. p. C1413-C21.
70. De Anda-Duran I, Kimbrough AD, Bazzano LA. HIV and hypertension epidemiology. Curr Opin Cardiol 2023; 38:297–303.
71. Kaluba L, Chikopela T, Goma F, *et al.* Vascular dysfunction and body mass index in African adults with HIV. BMC Cardiovasc Disord 2023; 23:64.
72. Masenga SK, Kirabo A, Hamooya BM, *et al.* HIV-positive demonstrate more salt sensitivity and nocturnal nondipping blood pressure than HIV-negative individuals. Clin Hypertens 2021; 27:1–10.
73. Mutengo KH, Masenga SK, Mwesigwa N, *et al.* Hypertension and human
■ immunodeficiency virus: a paradigm for epithelial sodium channels? Front Cardiovasc Med 2022; 9:968184.
This review discusses the potential role of altered ENaC activity in contributing to salt-sensitive hypertension in people with HIV.