

# Is the Sodium an Activator of Immune System in Hypertension?

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**Abbreviations:** APCs: Antigen Presenting Cells; AH: Arterial Hypertension; BP: Blood Pressure; DCs: Dendritic Cells; HS: High salt; IsoLG: Isolevuglandin; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; PBMCs: Peripheral Blood Mononuclear Cells; SGK1: Serum Glucocorticoid Regulated Kinase 1

## ABSTRACT

The sodium plays an essential role in human homeostasis and it has been described that a 30-50% of hypertensive patients are sensible to changes in their blood pressure after dietary high sodium intake. The last 20 years have been very active in trying to answer how the immune cells participate in hypertension, where the implications of increased sodium salt intake on the activation of the immune system have not been fully clarified. Even when some described mechanisms for macrophages, dendritic cells and lymphocytes proportion great insight for this understanding, the information concerning the different sodium compartments for its storage arise a new challenge for this area. This mini review highlights recent studies in different experimental settings regarding the effect of sodium as an activator for the immune system in hypertension and the mechanisms involved. We comment also the last studies suggesting the role of sodium as a regulator of immune cells in kidney medulla and extrarenal compartments that possibly may be involved in hypertension.

**Keywords:** Salt; Immune Cells; Sodium; Hypertension; Dendritic Cells; Macrophages; Lymphocytes; Kidney

## Introduction

The sodium is essential for life in humans, where its balance is determined mainly by kidney function and by it consume that depends on social culture and people behavior. The World Health Organization has recommended adjusting the dietary sodium salt intake, since different studies suggest that high salt (HS) diet is strongly associated with cardiovascular diseases and blood pressure (BP) rise. The relationship between salt intake and BP has been well-established based on clinical and pre-clinical studies [1]. For instance, the International Study of Sodium, Potassium, and Blood Pressure study – INTERSALT - demonstrated in 10,079 patients that exist a direct association between sodium intake and BP increase [2]. More recently, interventional studies show that salt intake reduction decreases levels of BP in normotensive and hypertensive patients [3,4], while a meta-analysis demonstrated that salt intake reduction in 2.5g/day is associated with a 20% diminution in cardiovascular events [5]. The BP rise after HS intake has been classically related to the restricted renal capacity

into excrete sodium, as consequence of the activation of the intrarenal renin-angiotensin aldosterone system and the reactive oxygen species formation [6-9]. In addition, HS intake may activate the sympathetic nervous system and to promote a direct vasoconstriction in blood vessels [10,11], supporting a neurogenic mechanism.

However, and even when the activation of immune system has been associated to human arterial hypertension (AH) since 60s [12], the implications of increased sodium salt intake on the activation of the immune system have not been clarified. Here, we highlight the effects of sodium and how its distribution may participate on the immune system activation during AH.

## Immune Cells in Hypertension

The hypothesis for a causal role of immune cells in AH was proposed in 2007 starting with the Guzik's study [13]. In the last 20 years, different experimental approaches have been performed

to evaluate how cells of the innate and adaptive immune systems participate in AH, where monocytes-macrophages [14], dendritic cells (DCs) [15,16], and lymphocytes [17-19] present experimental evidence that supports their participation in AH [20]. In relation to the mechanisms involved, it has been described that monocyte-macrophages act by increasing damage to target tissues [21], while DCs may produce isolevuglandin (IsoLG)-adduct, forming neoantigens after the activation of Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [22,23], promoting the activation of T-lymphocytes and the secretion of pro-inflammatory cytokines that favor to the sodium reabsorption and cardiovascular/renal damage [24]. Additionally, although other components of the innate immune system, such as neutrophils and the complement system, have been less involved (and studied), their potential role in the development of AH cannot be ruled out [25,26].

### Sodium Effect on Immune Cells in Hypertension

Early studies demonstrated that hypertonic salt solutions are able to increase cytokine production from human and rabbit peripheral blood mononuclear cells (PBMCs) [27], supporting the idea that the microenvironment is relevant for the pro-inflammatory phenotype in T lymphocytes and monocyte-macrophages [28]. Likewise, it was shown that the count of blood monocytes positively correlates with salt intake in normotensive patients [29]. Recently, Ruggeri et al. [30] demonstrated that CD14<sup>+</sup> monocytes isolated from human PBMCs present an increase in IsoLG-adducts, and a greater secretion of pro-inflammatory cytokines, when cells are exposed to a HS concentration (190mM of sodium chloride) [30]. Interestingly, this effect was prevented by inhibition of NADPH oxidase. In this study, the researchers observed that the transcriptome of monocytes exposed to a HS *In Vitro*, showed high expression of chemokine receptors and for pro-inflammatory cytokines, particularly interleukin-1 $\beta$  [30]. Together with other results, the authors suggest that a HS concentration promotes the activation of human monocytes mediated by NADPH oxidase and by the formation of IsoLG-adducts. In the same line, the authors demonstrated previously that the excess of dietary salt alters the gut microbiome leading to hypertension [31]. They found an increased accumulation of IsoLGs in the colon of hypertensive patients [31].

These findings were replicated in a murine model, where HS feeding also increased the IsoLG-adducts in mesenteric myeloid antigen-presenting cells (APCs), compared with animals that received normal salt diet [31]. The hypothesis proposes that sodium can enter to APCs via epithelial sodium channel (ENaC) leading to intracellular formation of IsoLGs, in a process regulated by the Serum and Glucocorticoid Kinase-1 (SGK1) and by NADPH oxidase [23,32]. This mechanism is quite interesting because suggest a new role for ENaC inhibition in the therapy for AH [33]. In addition, concerning to the role of CD14<sup>+</sup> in APCs, it has been proposed that CD14 may participate with female sex hormone

signaling modulating the pro-inflammatory activity favoring the salt-sensitive AH [34]. T lymphocytes favor the development of AH through the secretion of pro-inflammatory cytokines. *In Vitro* studies have shown that the increment of sodium salt concentration favors the T lymphocytes differentiation to T-helper (Th)<sub>17</sub> cells in a SGK1-dependent way [35,36]. In this same line, knockout mice for Sgk1 in CD4<sup>+</sup> cells showed a prevention in AH and less vascular/renal damage induced by angiotensin II and deoxycorticosterone-salt [37]. Interestingly, it has been observed that the expression of SGK1 is higher in Th<sub>17</sub> and T<sub>reg</sub> cells compared to other T lymphocytes [36], where the immunomodulatory capacity of Treg lymphocytes is inhibited by HS [38].

However, these evidence are not excluding the fact that sodium excess may activate other populations of Th lymphocytes [28], since the participation of CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes has been confirmed in different models of AH [20,39], indicating that SGK1 pathway could be a common signaling pathway within immune cells in salt-sensitive HA.

### Sodium Distribution and Its Possible Effects on Immune Response

In the last 15 years, new studies have aimed the clinical impact of sodium distribution and storage in body compartments. One of the most discussed tissues is the skin; it has been demonstrated that sodium accumulation in skin interstitium is bounded to glycosaminoglycans [40]. This is quite interesting since monocytes-macrophages are proposed to be regulators of subcutaneous lymphatic system through the tonicity-responsive enhancer binding protein and the vascular endothelial growth factor-C [41]. Additionally, this mechanism is considered pivotal for monocytes-macrophages mobilization when skin present a HS content, representing a modulatory way for BP in patients. New experimental data is needed for this potential mechanism since high skin sodium content has been directly associated with cardiac hypertrophy in kidney disease [42]. The tunica intima is proposed also as a source of non-osmotic sodium storage and as a contributor to salt sensitivity [43]. These observations may proportionate new rationale for to explain the heterogeneity of patients in BP changes after HS intake, and how the tunica intima damage may alter the sodium balance in closely related diseases to AH, such as renal disease and diabetes mellitus. However, new studies are necessary to determine how the endothelial cells in situation of HS may modulate the immune cells.

Finally, the kidney medulla it is well-recognized for represent a microenvironment with high osmolarity and sodium accumulation. The role of renal medulla on immunity is still controversial due to it hyperosmolarity has been reported to polarize APCs towards anti-inflammatory macrophages after renal transplant [44], suggesting that hypertonicity in renal medulla may modulate the pro-inflammatory status during kidney rejection or in the AH. By contrast, a study by Berry et al. [45], proposed that the hypersaline

microenvironment set up a bactericidal activity in the kidney, by showing a high production of chemoattractant proteins from tubular epithelial cells [45].

## Conclusion

In general, the available evidence suggest that increased local sodium levels can enhance the inflammatory potential of APCs, activating T lymphocytes, promoting inflammation and AH. We need additional studies in order to describe the possible effects of sodium on innate immune cells, and whether the renal medulla, skin interstitium and the tunica intima microenvironment play a role in AH. However, and even when our knowledge is limited, the recommendation of sodium adjustment for patients in order to avoid cardiovascular diseases remains absolutely necessary.

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## Conflict of Interest

None.

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