Sodium and its manifold impact on our immune system

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The Western diet is rich in salt, and a high salt diet (HSD) is suspected to be a risk factor for cardiovascular diseases. It is now widely accepted that an experimental HSD can stimulate components of the immune system, potentially exacerbating certain autoimmune diseases, or alternatively, improving defenses against certain infections, such as cutaneous leishmaniasis. However, recent findings show that an experimental HSD may also aggravate other infections (e.g., pyelonephritis or systemic listeriosis). Here, we discuss the modulatory effects of a HSD on the microbiota, metabolic signaling, hormonal responses, local sodium concentrations, and their effects on various immune cell types in different tissues. We describe how these factors are integrated, resulting either in immune stimulation or suppression in various tissues and disease settings.

Salt (NaCl) used to be so rare and valuable that in the 17th century for instance, the Duchy of Bavaria and the city of Salzburg entered into war over it. Even the word ‘salary’ reflects the preciousness that salt once had [1]. Due to geotechnological advances, salt nowadays is neither rare nor expensive. We love it and, thus, we eat a lot of it. Typical diets in Western countries and China contain more than 10 g per day [2].

The high salt content of diets in industrialized countries is suspected to be a risk factor that drives mortality and disease burden [3]. The connection between elevated salt consumption and hypertension was first proposed more than 50 years ago [4], and remains intensively discussed, especially since recent work questioned this connection [5]. Furthermore, recent studies have uncovered new links of salt to our health, especially through the proinflammatory effects of sodium [6–14]. On the one hand, HSD can stimulate certain components of the immune system, namely, to combat pathogens more efficiently [10,11,15] to fight cancer [12,13], or to elicit more vigorous autoimmune responses [6,16,17]. Moreover, HSD can boost osteoclast activity and thereby facilitate orthodontic tooth movement [18] and augment proinflammatory activation of microglia, which can aggravate stroke injury [19]. Of note, salt-losing tubulopathies (see Glossary) that result in sodium loss, have enhanced susceptibility to mucosal infections in humans [20]. Likewise, treating renal transplant patients with loop diuretics, which causes the excretion of sodium, can increase the incidence of urinary tract infections in these patients [21]. This has led to the current view that sodium is generally immunostimulatory depending on the local microenvironment [22,23]. On the other hand, recent findings have uncovered the immunosuppressive effects of sodium [24,25]. Thus, a comprehensive theory about when and where sodium is immunostimulatory or suppressive is wholly lacking at present.

Here, we wish to draw a broader picture of the complex systemic immune regulatory circuits induced by dietary sodium and its local effects. We discuss sodium uptake and tissue storage, local effects on immune cells, systemic effects through the microbiota and endocrine alterations, as well as specific effects in immune-mediated diseases and infections, with a focus on pyelonephritis. We hypothesize that a bird’s-eye view of immunology that encompasses anatomical, physiological, and
microbiological factors, may allow to predict the effects of a HSD on certain diseases, and may also reconcile reports in the literature that are seemingly contradictory.

**Dietary high salt and tissue sodium storage**

Theoretically, a HSD may affect our organism via direct or indirect, local or systemic effects (Figure 1A,B). Specifically, preclinical studies with rodents using experimental sodium-rich diets revealed that sodium can accumulate in skin, thymus, liver, and spleen [13,26–28] and, in addition, sodium may be potentially stored in endothelial surface layers [29], and thus act locally on surrounding cells. Moreover, there is evidence in mice that the kidney and bone marrow can lose salt upon dietary experimental HSD [24,30], and consequently, these tissues display a lower sodium content upon HSD than low salt diet (LSD). In general, HSD does not uniformly result in sodium accumulation in all tissues. In addition, these responses may depend on the genetic background of animals and organisms studied [15]. These findings highlight the importance of quantifying tissue sodium concentrations, and ideally chloride, in further studies addressing the local effects of these electrolytes under high salt diet or LSDs.

It is not completely clear why, when, or how sodium accumulates in tissues. Correlative analysis of glycosaminoglycan content, and its charge capacity in rodents [26,31,32] and humans [33], suggested that negatively charged glycosaminoglycans may at least partially contribute to tissue sodium accumulation by binding positively charged ions [26,31–33]. In addition, there is evidence from studies with rodents that this sodium storage in the skin generates a hypertonic environment [27]. How hypertonic fluid microdomains can be generated is unclear. One study modeled

![Figure 1. Direct and indirect changes induced by HSD.](image)

(A) HSD exposure leads to Na⁺ increase in the skin, thymus, liver, spleen, and urine, but decreases in the bone marrow and kidneys [13,24,26–28,30,45]. HSD diminishes ACTH, angiotensin II, testosterone, and processes such as glycolysis, while elevating urea, glucocorticoids, ketone body production, and fatty acid oxidation [24,45,46]. Moreover, HSD consumption results in reshaping the microbiota composition by reducing indole-3 lactic acid concentrations in the gut [65]. All these changes might be either immunostimulatory or immunosuppressive, depending on the nature of the change and the immune cell type exposed to it. Some of the alterations shown here were demonstrated in mice. A human body is shown for convenience. The illustration was created with BioRender.com. Abbreviations: ACTH, adrenocorticotropic hormone; HSD, high salt diet.
existing data and concluded that there might be a cutaneous countercurrent system similar to the kidney [34], allowing the generation of a hypertonic cutaneous fluid compartment rich in sodium. In this model, the lymphatics would represent a tubular/collecting duct-like system that drains sodium from the skin [34]. This model matches the findings that sodium content is substantially higher in cutaneous lymphatics of rodents compared to surrounding tissue [27]. In preclinical mouse and rat models, a HSD increased the compartment of circulating classical monocytes compared to a normal salt diet [35], and dermal macrophage numbers relative to LSD [26,27,36]. A mechanism was proposed in which cutaneous macrophages regulated the abundance of skin lymph capillaries [26,27]. Accordingly, osmoprotective signaling through the transcription factor nuclear factor of activated T cells 5 (NFAT5), also known as toxicity-responsive enhancer binding protein 5 (TonEBP) [37] in macrophages, removed excess sodium and prevented HSD-induced hypertension in these rodent models [26,27]. Of note, the exact role of NFAT5 and macrophages in local ionic balance has been reviewed elsewhere [22,26,38]. In humans, an experimental HSD (≥ 12 g NaCl/day for 7–14 days) also resulted in the accumulation of Na⁺ [39] and macrophages [40] in the skin, strongly suggesting that this system might be operative in humans as well.

It is unclear why sodium concentrations can be decreased in the bone marrow upon HSD exposure in mice [30]. Perhaps processes of well hematopoiesis and cell proliferation might require lower sodium concentrations than immune cell activation, given that higher tissue osmolality may be encountered by infiltrating immune cells such as dendritic cells (DC) and T cells in secondary lymphatics [13,41]. In line with this, relative to controls, increased toxicity in cancer cell lines has augmented the effect of osmolytic activity of death receptors [42] which are involved in hematopoiesis as well [43]. Of note, mice consuming a LSD did not show higher sodium in the bone marrow if myeloid cells did not express NFAT5 [30], suggesting that this transcription factor might contribute to mediating sodium accumulation in this organ. However, as these possibilities remain speculative, further studies are needed to understand regulatory circuits involving sodium in the bone marrow.

By contrast, a sodium loss in the kidneys of mice fed a HSD might be explained by available knowledge; under normal conditions, the kidney uses sodium and urea to create an osmotic gradient between the kidney cortex and the medulla, to reabsorb water from the glomerular filtrate [44]. Under a HSD, the kidneys excrete excess sodium by switching off sodium reabsorption [45,46]. Instead, in this situation, the kidney preferentially uses organic osmolytes to establish the osmotic gradient, especially urea, a process referred to as ‘urea-dependent water conservation’ [45]. Thus, during a HSD, the renal medulla is rich in urea, while sodium concentrations decrease [24]. However, mechanistic insight for sodium storage in other tissues remains poorly understood.

**Diet-independent sodium accumulation and impact on immune cells**

Sodium tissue accumulation can also occur in a diet-independent manner. Human long-lasting sodium balance studies demonstrate that under resting conditions, total body sodium concentrations follow an infradian rhythmicity that is under hormonal control [47]. Infection and inflammation can cause sodium build-up in affected human and mouse skin tissues in a diet-independent manner [10,48,49]. Increased sodium concentrations have been found in brain lesions of multiple sclerosis patients [50], fibrotic skin in patients with diffuse cutaneous systemic sclerosis [51], and in the skin of patients with lipedema [52] relative to healthy controls. Furthermore, there is evidence from noninvasive, 23Na-MRI imaging that sodium concentrations in cancerous human brain and breast tissue are increased as well, relative to controls [53,54]. Overall, the mechanisms contributing to diet-independent local sodium accumulation are ill-defined. It is reasonable to speculate that sodium...
changes reflect an inflammation-triggered reprogramming of the extracellular tissue matrix [34,38,55]. In addition to local tissue sodium accumulation, there is evidence in a model of isolated guinea pig trachea that hypertonic conditions exist in the airways on mucosal surface liquids due to water evaporation under steady state conditions [56]. Therefore, alveolar macrophages might be especially well adapted to operate in sodium-rich environments. Overall, these findings demonstrate that in addition to dietary factors, inflammatory conditions and local anatomical peculiarities might also affect the local sodium balance.

For several years, interest has been growing to understand the impact of these ionic tissue signals on immune cell responses. Indeed, immune cells are not only equipped to adjust to these sodium-rich microdomains, but salt conditions can also profoundly influence the functions of immune cells [22,23,38]. For instance, high salt conditions enhance the proinflammatory activation of mouse macrophages, while limiting their anti-inflammatory potential [6–9,12–14]. Likewise, sodium-rich environments have been reported to favor the development of inflammatory IL-17-producing CD4+ T cells (Th17) under Th17 polarizing experimental conditions in mice and humans [16,17,25,49] and to block the immunosuppressive activity of human regulatory T cells [57]. In the absence of proinflammatory Th17-skewing conditions, however, high sodium can favor the development of Th helper 2 responses from human naive and memory T cells [49] or able to induce regulatory outputs in human and mouse Th17 cells [25]. These findings suggest that sodium-induced effects on T cells are contextual. These various sodium-triggered T cell responses can involve osmoprotective signaling, including NFAT5 and/ or serum and glucocorticoid regulated kinase 1-dependent signal transduction [16,17,25,49,57]. Therefore, the molecular underpinnings driving these divergent T cell responses require further molecular investigation.

The mechanisms of how immune cells can detect increased sodium concentrations are largely elusive. In contrast to epithelial cells, immune cells lack an apical-basal axis orientation, indicating that their ability to handle changes in the local ionic composition will differ from the mechanisms in epithelial cells. In addition, in macrophages for instance, the resting membrane potential is not as negative as in epithelial cells [58,59], which has implications on the activity and thermodynamics of channels, exchangers, and transporters. Our group reported that the Na+/Ca2+ exchanger plays an important role in the detection of increases in local extracellular sodium levels and contributes to amplifying proinflammatory mouse macrophage responses [58]. However, sodium handling ensuing cellular responses remain undetermined and we do not know how other immune cells might detect and/or handle excess sodium amounts. Of note, in juvenile Japanese eels (Anguilla japonica), a sodium-binding system exists that allows the organism to adapt to acute sodium-rich environments [60]. Whether similar systems exist in mammals requires further investigation.

In mouse macrophages, local increases in sodium do not only boost their inflammatory potential but also enhance their antimicrobial activity. While HS-augmented defenses against the protozoan parasite Leishmania major hinged on the increased NFAT5-dependent production of leishmanicidal nitric oxide (NO) in a mouse model of cutaneous leishmaniasis [10], HS-boosted antibacterial responses in mouse macrophages required autophagy and targeting of intracellular bacteria to acidic autolysosomes [61]. While NFAT5 coordinated the subcellular targeting of bacteria to autolysosomal structures in mouse macrophages, enhanced expression of components of the autophagy machinery depends on the transcription factor hypoxia-inducible factor 1α (HIF1α) (Figure 2) [61]. Autophagy and HIF1α-dependent signaling are both linked to metabolism, and a recent study reported an important role of sodium in mitochondrial energy generation in bovine aortic endothelial cells and mouse embryonic fibroblasts [62]. Therefore, this suggested that sodium might reprogram metabolic and cellular energetics, which might ultimately impact inflammatory outputs and the handling of sodium. Given that metabolic signaling is recognized as
an important immune regulator, it will be interesting to further investigate any potential interactions between sodium handling and immunometabolism.

**A HSD can affect the gut microbiome and microbiota-derived tryptophan metabolites**

Only recently have we started to understand how the intestinal microbiota and its metabolites impact the host and contribute to health or disease. The gut microbiota is now regarded as an endocrine organ generating metabolites affecting host physiology, and triggering responses in the local microenvironment or distant target organs [63]. While the impact of high fat and sugar on the gut microbiome has been extensively studied, the effect of high salt was only recently described: in mice, a high fat diet can lead to a profound shift in the composition of the gut microbiome [64], and a HSD modifies the gut microbiome to a much lesser extent, particularly when depleting *Lactobacillus* spp [65]. In addition, a HSD can also decrease microbial populations across a variety of genera including *Oscillibacter, Pseudolavonifractor, Clostridium XIVa, Johnsonella, and Rothia* [65]. With a HSD, other genera such as *Parasutterella* spp. are increased in the intestine [65]. Along with an altered gut microbiome, a HSD increases systolic blood pressure in mice, as well as clinical symptoms (paralysis score) of experimental autoimmune encephalomyelitis (EAE), and also the frequency of Th17 cells in the gut, spleen, and spinal cord [65]. Besides its pivotal role in the generation of autoimmunity, Th17 cells also play a role in hypertension [66]. Moreover, *Lactobacilli* are able to metabolize the essential amino acid tryptophan to indole metabolites [67], and thus, it might not be surprising that a HSD, beside its suppressive action...
on *Lactobacillus* abundance, can also reduce fecal indole metabolites [65]. Conversely, probiotic *Lactobacillus* treatment in mice increases fecal indole-3 metabolites, together with a reduction in Th17 numbers, systolic blood pressure, and experimental autoimmunity in this EAE model. Mechanistically, indole-3 lactic acid inhibited Th17 polarization, suggesting that tryptophan metabolites might act as Th17 inhibitors [65]. In line with these data, in another study, a HSD also accelerated experimental colitis in mice by decreasing intestinal *Lactobacillus* abundance and short-chain fatty acid butyrate production [68]. Of note, a modest reduction in oral sodium intake in therapy-naïve hypertensive humans has resulted in an increase in serum short-chain fatty acids, which are also associated with reduced blood pressure and arterial stiffness [69]. Altogether, high dietary sodium intake can alter the gut microbiota and consequently, the concentration of microbiota-derived metabolites. As these altered metabolites are absorbed into the mucosa micromilieu, they may locally affect gut immune homeostasis. This in turn, may have consequences for the host and influence disease pathogenesis in certain inflammatory, autoimmune, and cardiovascular diseases.

**A HSD has systemic endocrine effects that can indirectly affect immunity**

A HSD not only alters systemic immunity by modifying microbiota-derived metabolites but can also influence the endocrine system. Hormones of the renin-angiotensin aldosterone system are downregulated during a HSD, and facilitate excess sodium excretion by the kidney [70]. Some of these hormones have immunoregulatory properties. Thus, angiotensin II has been reported to increase natural killer (NK) cell cytotoxic activity, monocyte, and neutrophil chemotaxis, as well as human DC and T helper cell functions [71]. In addition, aldosterone promoted the activation of proinflammatory macrophages, resulting in elevated reactive oxygen species (ROS) production, increased Th17 polarization, and boosted CD8+ T cell activation *in vitro* [72–75]. Moreover, aldosterone has stimulated human neutrophil degranulation and release of myeloperoxidase [76,77]. Given that a HSD can reduce aldosterone concentrations, it is reasonable to hypothesize that its effects on immunity might be reduced during a HSD intake, but to our knowledge, this has not been tested, and whether this effect on aldosterone has consequences for the induction of immune-mediated diseases or anti-infectious defense is unknown.

From another angle, glucocorticoids are increased during a HSD in mice and humans [24,45,46]. Studies in mice have revealed this to be a direct consequence of the downregulation of aldosterone synthase [24], which causes the accumulation of corticosterone, an aldosterone precursor with glucocorticoid functionality [78]. Of note, corticosterone concentrations did not follow the diurnal rhythm that glucocorticoids normally display, and this rhythm has been shown to influence immune cells in a complex manner [79]. Moreover, corticosterone stimulates ketogenesis in the liver and promotes the production of urea [45]. As mentioned previously, during a HSD, urea establishes a renal osmotic gradient for water retention, since excess sodium needs to be excreted [45,46].

Specifically, glucocorticoids can affect immune cells differently; for instance, they inhibit neutrophil-mediated phagocytosis (pathogen clearance), but stimulate mononuclear phagocyte-mediated phagocytosis (e.g., dead neutrophil clearance) [80]. Furthermore, glucocorticoids suppress bacterial digestion by neutrophils, but not by macrophages *in vitro* [24]. Therefore, despite the general anti-inflammatory properties of glucocorticoids, these modulators may differentially influence immune responses carried out primarily by macrophages or neutrophils.

Similarly to sodium, glucocorticoids can augment NFAT5 expression [24]. Thus, the increase of NFAT5 expression often seen under a HSD, might be at least partially be a consequence of hyperglucocorticoidism, although this remains speculative. However, if true, it might help to explain why NFAT5 increases in tissues that do not accumulate sodium under a HSD, such as the kidney [24].
In summary, a HSD can decrease the concentrations of hormones with proinflammatory properties, such as angiotensin, aldosterone, and adrenocorticotropic hormone (ACTH), while in some cases, causing immunosuppressive hyperglucocorticoidism. As the effects appear to be cell type-dependent, the outcome of a HSD may hinge on the immune cell type involved in a given physiologic process, which may subsequently influence the outcome of a disease, or not.

Local and systemic effects of a HSD on pyelonephritis

Urinary bacterial infections occur frequently in daily clinical practice [81]. Ascending urinary tract infections can cause pyelonephritis, a life-threatening kidney infection [82]. Neutrophils are key in innate antimicrobial defense against urinary tract infections; they phagocytose and clear uropathogenic *Escherichia coli* (UPEC), while mononuclear phagocytes such as macrophages or DCs play an important role in neutrophil attraction and activation [81,83,84].

The functionality of mononuclear phagocytes differs in the kidney cortex and medulla [85], and the high medullary osmolarity is thought to be a responsible factor [82,86]. Medullary mononuclear phagocytes exposed to high sodium microenvironments have been reported to skew cells towards an anti-inflammatory state in human transplant rejection [87], and to reduce their antigen presentation capacity [88]. By contrast, based on the general view that sodium might stimulate these immune cells via NFAT5, it has been proposed that this ion might establish an intrarenal antibacterial defense zone in the renal medulla, thereby promoting defense against pyelonephritis [9]. This conclusion was supported by experiments demonstrating aggravated pyelonephritis in mice treated with diuretics to disrupt the osmotic gradient or after systemic genetic deletion of NFAT5 [9]. However, the particular diuretics used, tolvaptan and demeclocycline, interfered with water retention in the collecting duct, and whether they disrupted the intrarenal osmotic gradient was not tested [9]. Moreover, NFAT5 is required for cellular resistance against osmotic stress [89], and the hyperosmolar medullary environment might render NFAT5-deficient kidney cells more vulnerable to bacterial infections [9]. The authors suggested that this sodium-rich zone in the kidney might be beneficial in situations of dehydration, when the kidney increases the corticomedullary osmotic gradient, for example by accumulating sodium. Also this has not been experimentally tested, but if true, it might strengthen renal antimicrobial activity by macrophages [9]. However, the key immune effectors in pyelonephritis are neutrophils whose antimicrobial function, in contrast to macrophages, is not boosted by sodium [24]. Thus, increasing sodium concentrations in the renal medulla might not stimulate the type of immunity needed against pyelonephritis. In particular, it must be emphasized that achieving this increase by restricting fluid intake [9] might be counterproductive, because it would compromise the flushing of bacteria from the kidney. Indeed, we argue that the traditional medical advice to drink much fluid during pyelonephritis is still valid, and this opinion is supported by many clinical studies [84,87,90,91].

During consumption of a HSD, the intrarenal microenvironment changes dramatically [24]. Consequently, a state of pyelonephritis can be aggravated, as shown in mice under a HSD. This exacerbation was shown to be due to two effects that led to suppressed neutrophil effector functions [24]. First, the HSD-induced downregulation of the renin–angiotensin–aldosterone system (RAAS) reduced the sodium concentrations in the renal medulla, where instead the chaotropic compound urea accumulated [45]. Urea in turn inhibited neutrophil function, presumably by interfering with the actin skeleton [92]. Second, the glucocorticoids produced because of downregulated aldosterone synthesis suppressed neutrophil functions directly, both locally in a murine pyelonephritis model and systemically in a *Listeria monocytogenes* mouse infection model. Suppressed neutrophil functions were also noted in humans consuming a HSD for only one week [24] (Figure 3).
These changes in sodium and glucocorticoids seemed to provide an explanation, at least in part, as to why intake of a HSD had diametric effects on immunity against two infections, cutaneous *Leishmania* and bacterial pyelonephritis. On the one hand, sodium accumulation in the skin boosted activation of dermal macrophages in mice, important for fighting leishmaniasis [93,94], while neutrophils could be detrimental [95]. In the kidney, sodium was decreased and urea increased, and the latter suppressed neutrophils, important for fighting pyelonephritis [24]. On the other hand, the HSD-induced hyperglucocorticoidism suppressed bactericidal neutrophil activity, and thereby defenses against pyelonephritis, but did not suppress macrophages, and hence, the defense against *Leishmania* was not compromised [10]. Thus, by integrating the local and cell-type specific effects of sodium versus glucocorticoids, it may be possible to reconcile the seemingly contradictory effects of HSD consumption on the defense against an infection such as leishmaniasis (in the skin), versus one such as pyelonephritis (in the kidney).

**Concluding remarks**

Here, we have discussed potential inhibition and activation mechanisms as well as outcomes for consuming a HSD, and its effects on cells of the immune system, and ultimately, on tissue/organ homeostasis. The effects of a HSD on immune responses depends on several factors, for example, the organ or tissue examined. In mammals, a HSD can increase sodium in the skin, but reduce it in the kidney and bone marrow, with obvious consequences for cells that are responsive to sodium. A second factor is the target immune cell being affected by a HSD. Macrophages and T cells, but not neutrophils, can be activated by sodium. Thus far, the literature has shown that a HSD can stimulate certain branches of innate or adaptive immunity, for example, to fight diseases such as parasite infections, in which mononuclear phagocytes are crucial, but in which neutrophils may not be important or as relevant. Until now, we have no comprehensive picture on the importance of the microbiome on salt-induced immunomodulation. Hygiene regimes of different laboratories might crucially affect the response of sodium-rich diets on the immune system. In line with this, research in wildling mice, diverse in the microbial makeup compared to ‘clean’ laboratory mice, may mimic some human disease phenotypes better than current experimental models [96]. In addition, the content of sodium in the chow and drinking water...

**Outstanding questions**

What are the concentrations of ions and osmolytes in tissues that have not been closely examined (e.g., skin or kidney) in health, disease, and upon dietary challenges? A comprehensive picture of these electrolyte changes would be a valuable resource for future studies in this field.

Which mechanisms account for the regulation of local sodium balance in tissues? Recent work uncovered that this regulation is more complex than previously thought and a complete theory of the underlying mechanisms might also improve our understanding of sodium regulatory effects on immunity.

Can local Na⁺ cell/tissue storage be affected by reducing dietary salt intake? This is an obvious question which remains unresolved.

How are sodium concentrations sensed and interpreted by immune cells? A mechanism for macrophages has been shown, but other immune cells may use other mechanisms.

How do HSD-altered mineralocorticoid and glucocorticoid concentrations affect the progression of inflammatory diseases mediated by immune cells sensitive to these hormones, such as gout?

How quickly can HSD-induced systemic changes and their repercussions normalize after salt intake reduction?

What are the effects of combining a HSD with high sugar, fat, and protein diet on immune cells? A typical Western diet contains too many of these nutrients and in combination, might potentially have stronger or distinct effects on immunity.
under regular (so-called normal salt) conditions is not monitored regularly and might also introduce additional experimental variation. A third factor are glucocorticoids, which are systemically elevated during a HSD. Some immune effector cells, like neutrophils, are suppressed by glucocorticoids [97], whereas some functions of macrophages are even stimulated [98]. A fourth factor concerns the alterations that occur in gut microbiome-derived metabolites under a HSD, as these molecules may possess immunoregulatory properties, affecting the physiological homeostasis (or disease state) of an organism in a context-, organ-, and immune cell type-specific manner.

We posit that the effects of a HSD in one specific disease cannot be simply extrapolated to other conditions with other immune cells or other anatomical sites involved. However, when the anatomical, physiological, and microbiological conditions are known, it is possible to predict whether a HSD might aggravate or attenuate a disease state for specific pathologies and to reconcile conflicting data in the literature. Much information to this end is available already, but many questions remain that need to be answered (see Outstanding questions).

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References
1. Kurlansky, M. (2010) Salt, Walker Books
2. Tan, Monique et al. (2019) Twenty-four-hour urinary sodium and potassium excretion in China: a systematic review and meta-analysis. J. Am. Heart Assoc. 8, e01352
3. Cook, N.R. et al. (2016) Sodium intake and all-cause mortality over 20 years in the trials of hypertension prevention. J. Am. Coll. Cardiol. 68, 1609–1617
4. Titze, J. and Luft, F.C. (2017) Speculations on salt and the state of arterial hypertension. Kidney Int. 91, 1324–1335
5. Messeri, F.H. et al. (2000) Sodium intake, life expectancy, and all-cause mortality. Eur. Heart J. 21, 894–904
6. Hucke, S. et al. (2016) Sodium chloride promotes pro-inflammatory macrophage polarization thereby aggravating CNS autoimmunity. J. Autoimmun. 67, 90–101
7. Ip, W.K.E. and Medzhitov, R. (2015) Macrophages monitor tissue osmolarity and induce inflammatory response through NLRP3 and NLR4 inflammasome activation. Nat. Commun. 6, 6931
8. Zhang, W.-C. et al. (2015) High salt primes a specific activation state of macrophages. MNIJ. Cell Res. 25, 892–910
9. Berry, M.R. et al. (2017) Renal sodium gradient orchestrates a dynamic antimicrobial defense zone. Cell 170, 860–874.e19
10. Jantsch, J. et al. (2015) Cutaneous Na+ storage strengthens the antimicrobial barrier function of the skin and boosts macrophage-driven host defense. Cell Metab. 21, 490–501
11. Zhang, W.-C. et al. (2018) Elevated sodium chloride drives type I interferon signaling in macrophages and increases antiviral resistance. J. Biol. Chem. 293, 1030–1039
12. Willebrand, R. et al. (2019) High salt inhibits tumor growth by enhancing antitumor immunity. Front. Immunol. 10, 1141
13. He, W. et al. (2020) High-salt diet inhibits tumour growth in mice via regulating myeloid-derived suppressor cell differentiation. Nat. Commun. 11, 1732
14. Binger, K.-J. et al. (2015) High salt reduces the activation of IL-4- and IL-13-stimulated macrophages. J. Clin. Invest. 125, 4223
15. de Oliveira, C.B.S. et al. (2018) The influence of salt intake on the course of experimental toxoplasmosis in outbred or inbred mouse strains. Rev. Patol. Trop. J. Trop. Pathol. 47, 87–99
16. Kleinewietfeld, M. et al. (2013) Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. Nature 496, 518–522
17. Wu, C. et al. (2013) Induction of pathogenic TH17 cells by inducible salt-sensing kinase SIK1. Nature 496, 513–517
18. Schröder, A. et al. (2021) Dietary salt accelerates orthodontic tooth movement by increased osteoclast activity. Int. J. Mol. Sci. 22, 596
19. Zhang, T. et al. (2020) Excess salt intake promotes M1 microglia polarization via a p38/MAPK/AR-dependent pathway after cerebral ischemia in mice. Int. Immunopharmacol. 81, 106176
20. Evans, R.D.R. et al. (2020) Inherited salt-losing tubulopathies are associated with immunodeficiency due to impaired IL-17 responses. Nat. Commun. 11, 4369
21. Casper, J. et al. (2018) Renal transplant recipients receiving loop diuretic therapy have increased urinary tract infection rate and altered mediulary macrophage polarization marker expression. Kidney Int. 94, 963–1001
22. Schatz, V. et al. (2017) Elementary immunology: Na+ as a regulator of immunity. Pediatr. Nephrol. 32, 201–210
23. Wick, N. et al. (2018) The role of sodium in modulating immune cell function. Nat. Rev. Nephrol. 15, 540–555
24. Jobin, K. et al. (2020) A high-salt diet compromises antibacterial neutrophil responses through hormonal perturbation. Sci. Transl. Med. 12, eaay3850
25. Matthies, J. et al. (2020) Salt generates anti-inflammatory Th17 cells but amplifies pathogenicity in proinflammatory cytokine microenvironments. J. Clin. Invest. 130, 4587–4600
26. Machnik, A. et al. (2009) Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. Nat. Med. 15, S45–S52

27. Wigg, H. et al. (2013) Immune cells control skin lymphatic electrolyte homeostasis and blood pressure. J. Clin. Invest. 123, 2803–2815

28. Titz, J. et al. (2003) Osmotically inactive skin Na+ storage in rats. Am. J. Physiol. Renal Physiol. 285, F1108–F1117

29. Olde Engberink, R. H. G. et al. (2020) Clinical impact of tissue sodium storage. Pediatr. Nephrol. 35, 1373–1380

30. Schröder, A. et al. (2019) Osteoprotective action of low-salt diet requires myocard cell-derived NFAT5. JCI Insight 4, e127988

31. Titz, J. et al. (2004) Glycosaminoglycan polymerization may enable osmotically inactive Na+ storage in the skin. Am. J. Physiol. Heart Circ. Physiol. 287, H203–H208

32. Schaffthaler, M. et al. (2007) Mobilization of osmotically inactive Na+ by growth and by dietary salt restriction in rats. Am. J. Physiol. Renal Physiol. 296, F1450–F1500

33. Fischereider, M. et al. (2017) Sodium storage in human tissues is mediated by glycosaminoglycan expression. Am. J. Physiol. Renal Physiol. 313, F319–F325

34. Hinslisher, L. H. (2015) Tissue sodium storage: evidence for kidney-like extrarenal countercurrent systems? Pflugers Arch. 467, 551–568

35. Fan, A. et al. (2020) High-salt diet decreases mechanical threshold in mice that is mediated by a CCR2-dependent mechanism. J. Neuroinflammation 17, 179

36. Machnik, A. et al. (2010) Mononuclear phagocyte system depletion blocks intestinal toxicity-response enhancer binding protein vascular endothelial growth factor C expression and induces salt-sensitive hypertension in rats. Hypertension 55, 755–761

37. Choi, S.Y. et al. (2020) The evolving role of TonEBP as an immunometabolic stress protein. Nat. Rev. Nephrol. 16, 352–364

38. Müller, D. N. et al. (2019) Sodium in the microenvironment regulates immune responses and tissue homeostasis. Nat. Rev. Immunol. 19, 240–254

39. Sekarajah, V. et al. (2017) Novel mechanism for buffering dietary salt in humans: effects of salt loading on skin sodium, vascular endothelial growth factor C, and blood pressure. Hypertension 70, 900–907

40. Wenstedt, E.F.E. et al. (2019) Salt increases monocyte CCR2 expression and inflammatory responses in humans. JCI Insight 4, e130508

41. Zei, W.Y. et al. (2004) Nfat5/TonEBP mutant mice define osmotic stress as a critical feature of the lymphoid microenvironment. Proc. Natl. Acad. Sci. U. S. A. 101, 10673–10678

42. Sirt, S. et al. (2018) Hyperoncotic-enhanced BCL-2 addiction unleashes the cytotoxic potential of death receptors. Oncogene 37, 4122–4138

43. Zauli, G. and Secchiero, P. (2006) The role of the TRAIL/TRAIL receptor system in hematopoiesis and endothelial cell biology. Cytokine Growth Factor Rev. 17, 249–257

44. Dantle, W.H. et al. (2014) Urine-concentrating mechanism in the inner medulla: function of the thin limbs of the loops of Henle. Clin. J. Am. Soc. Nephrol. 9, 1781–1789

45. Kitadai, K. et al. (2017) High-salt intake reprogrammes cancer and energy metabolism for body fluid conservation. J. Clin. Invest. 127, 1944–1959

46. Rakova, N. et al. (2017) Increased salt consumption induces body water conservation and decreases fluid intake. J. Clin. Invest. 127, 1952–1963

47. Rakova, N. et al. (2013) Long-term space flight simulation reveals intradialytic variability in human Na+ balance. Cell Metab. 17, 125–131

48. Schwartz, L. et al. (2009) Is inflammation a consequence of extracellular hyperosmolarity? J. Inflamm. (Lond.) 6, 21

49. Matthias, J. et al. (2019) Sodium chloride is an ionic checkpoint for human TH2 cells and shapes the atopic skin microenvironment. Sci. Transl. Med. 11, eaau0683

50. Inglese, M. et al. (2010) Brain tissue sodium concentration in multiple sclerosis: a sodium imaging study at 3 tesla. Brain 133, 847–857

51. Kopp, C. et al. (2017) Na+ deposition in the fibrotic skin of systemic sclerosis patients detected by 23Na magnetic resonance imaging. Rheumatology (Oxford) 56, 556–560

52. Crescenzi, R. et al. (2018) Tissue sodium content is elevated in the skin and subcutaneous adipose tissue in women with lichen sclerosus. Obesity (Silver Spring) 26, 310–317

53. Ouwerkerk, R. et al. (2007) Elevated tissue sodium concentration in malignant breast lesions detected with noninvasive 23Na MRI. Breast Cancer Res. Treat. 105, 151–160

54. Leslie, T.K. et al. (2019) Sodium homeostasis in the tumour microenvironment. Biochim. Biophys. Acts (BBA) Rev. Cancer 1872, 188304

55. Bomans, C. et al. (2014) Remodelling the extracellular matrix in development and disease. Nat. Rev. Mol. Cell Biol. 15, 786–801

56. Shepherd, K.L. and Rahmouni, H. (1994) Evaporation-induced changes in airway surface liquid on an isolated guinea pig trachea. J. Appl. Physiol. (1985) 78, 1156–1165

57. Hernandez, A.L. et al. (2015) Sodium chloride inhibits the suppressive function of FOXP3 regulatory T cells. J. Clin. Invest. 125, 4212–4222

58. Neubert, P. et al. (2020) NCK1 represents an ionic Na+ sensing mechanism in macrophages. PLoS Biol. 18, e2000722

59. Hulsmans, M. et al. (2017) Macrophages facilitate electrical conduction in the heart. Cell 169, 510–522.e20

60. Wong, M.K.S. et al. (2017) A sodium binding system alleviates acute salt stress during seawater acclimation in eels. Zool. Lett. 3, 22

61. Neubert, P. et al. (2019) HIF-1A and Nfat5 coordinate Na+-boosted antibacterial defense via enhanced autophagy and autolysosomal targeting. Autophagy 15, 1999–1916

62. Herrsanz-Agustín, P. et al. (2020) Na+ controls hypoxic signalling by the mitochondrial respiratory chain. Nature 586, 267–271

63. Zhang, L.S. and Davies, S.S. (2016) Microbial metabolism of dietary components to bioactive metabolites: opportunities for new therapeutic interventions. Genome Med. 8, 46

64. Ang, G.Y. et al. (2022) Ketogenic diets alter the gut microbiome resulting in decreased intestinal TH17 cells. Cell 181, 1263–1275.e16

65. Wick, N. et al. (2017) Salt-responsive gut commensal modulates TH17 axis and disease. Nature 551, 585–589

66. Madhur, Meena S. et al. (2010) Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. Hypertension 55, 500–507

67. Zelante, T. et al. (2013) Tryptophan catabolites from microbiota engage anhydrocorticotropin receptor and balance mucosal reactivity via interleukin-22. Immunity. 39, 372–385

68. Miranda, P.M. et al. (2018) High salt diet exacerbates colitis in mice by decreasing Lactobacillus levels and butyrate production. Microbiome 6, 27

69. Chen, L. et al. (2002) Modest sodium reduction increases circulating short-chain fatty acids in untreated hypertensives: a randomized, double-blind, placebo-controlled trial. Hypertension 76, 73–79

70. Drenjanščič-Periči, I. et al. (2011) High-salt diet and hypertension: focus on the renin-angiotensin system. Kidney Blood Press. Res. 34, 1–11

71. Chang, Y. and Wei, W. (2015) Angiotensin II in inflammation, immunity, and rheumatoid arthritis. Clin. Exp. Immunol. 179, 137–145

72. Usher, M.G. et al. (2010) Myeloid mineralocorticoid receptor controls macrophage polarization and cardiovascular hypertrophy and remodeling in mice. J. Clin. Invest. 120, 3350–3364

73. Sun, Y. et al. (2002) Aldosterone-induced inflammation in the rat heart: role of oxidative stress. Am. J. Pathol. 161, 1773–1781

74. Gilbert, K.C. and Brown, N.J. (2010) Aldosterone and inflammation. Curr. Opin. Endocrinol. Diabetes Obes. 17, 199–204

75. Herrada, A.A. et al. (2010) Aldosterone promotes autoimmune damage by enhancing Th17-mediated immunity. J. Immunol. 184, 191–202

76. Díaz, D. et al. (2012) Aldosterone stimulates a degranulation response in human neutrophils: role of protein disulflde isomerase. Blood 120, 1034
77. Rivera, A. et al. (2013) Aldosterone stimulates neutrophils leading to increased β-glucuronidase, protein disulfide isomerase and myeloperoxidase secretion. Blood 122, 2271
78. Payne, A.H. and Hales, D.B. (2004) Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones. Endocr. Rev. 25, 947–970
79. Shimba, A. and Ikuta, K. (2020) Glucocorticoids regulate circadian rhythm of innate and adaptive immunity. Front. Immunol. 11, 2143
80. Piemonti, L. et al. (1999) Glucocorticoids increase the endocytic activity of human dendritic cells. Int. Immunol. 11, 1519–1526
81. Flores-Mireles, A.L. et al. (2015) Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat. Rev. Microbiol. 13, 269–284
82. Godaly, G. et al. (2016) Urinary tract infection molecular mechanisms and clinical translation. Pathogens 5, 24
83. Schivon, M. et al. (2014) Crosstalk between sentinel and helper macrophages permits neutrophil migration into infected uroepithelium. Cell 156, 456–468
84. Kolarczewska, E. and Kubies, P. (2013) Neutrophil recruitment and function in health and inflammation. Nat. Rev. Immunol. 13, 159–175
85. Hochheiser, K. et al. (2013) Exclusive CX3CR1 dependence of kidney DCs impacts glomerulonephritis progression. J. Clin. Invest. 123, 4240–4254
86. Kuts, C. et al. (2013) The immune system and kidney disease: basic concepts and clinical implications. Nat. Rev. Immunol. 13, 738–753
87. Chessa, F. et al. (2016) The renal microenvironment modifies dendritic cell phenotype. Kidney Int. 89, 82–94
88. Popovic, Z.V. et al. (2017) Hyperosmolality impedes the cross-priming competence of dendritic cells in a TRIF-dependent manner. Sci. Rep. 7, 311
89. Lee, S.D. et al. (2011) TonEBP stimulates multiple cellular pathways for adaptation to hypertonic stress: organic osmolyte-dependent and-independent pathways. Am. J. Physiol. Renal Physiol. 300, F707–F715
90. Nygaard, I. and Linder, M. (1997) Thirst at work—an occupational hazard? Int. Urogynecol. J. Pelvic Floor Dysfunct. 8, 340–343
91. Tian, Y. et al. (2016) Water consumption and urinary tract infections: an in vitro study. Int. Urol. Nephrol. 48, 949–964
92. Kumemoto, R. et al. (2011) Effects of urea and guanidine hydrochloride on the sliding movement of actin filaments with ATP hydrolysis by myosin molecules. J. Biochem. 149, 719–720
93. Olekhnovitch, R. and Bousso, P. (2015) Induction, propagation, and activity of host nitric oxide: lessons from Leishmania infection. Trends Parasitol. 31, 653–664
94. Bogdan, C. (2015) Nitric oxide synthase in innate and adaptive immunity: an update. Trends Immunol. 36, 161–178
95. Laskay, T. et al. (2003) Neutrophil granulocytes—Trojan horses for Leishmania major and other intracellular microbes? Trends Microbiol. 11, 210–214
96. Rosshart, S.P. et al. (2019) Laboratory mice born to wild mice have natural microbiota and model human immune responses. Science 365, eaaw4361
97. Fuenfer, M.M. et al. (1975) Effect of various corticosteroids upon the phagocytic bactericidal activity of neutrophils. Surgery 78, 27–33
98. van der Goes, A. et al. (2003) Dexamethasone promotes phagocytosis and bacterial killing by human monocytes/macrophages in vitro. J. Leukoc. Biol. 67, 801–807