Hypertension

REVIEW

Sodium as an Important Regulator of Immunometabolism

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ABSTRACT: Salt sensitivity concerns blood pressure alterations after a change in salt intake (sodium chloride). The heart is a pump, and vessels are tubes; sodium can affect both. A high salt intake increases cardiac output, promotes vascular dysfunction and capillary rarefaction, and chronically leads to increased systemic vascular resistance. More recent findings suggest that sodium also acts as an important second messenger regulating energy metabolism and cellular functions. Besides endothelial cells and fibroblasts, sodium also affects innate and adaptive immunometabolism, immune cell function, and influences certain microbes and microbiota-derived metabolites. We propose the idea that the definition of salt sensitivity should be expanded beyond high blood pressure to cellular and molecular salt sensitivity. ***(Hypertension.* 2024;81:426–435. DOI: 10.1161/HYPERTENSIONAHA.123.19489.)** •

Key Words: macrophages ■ mitochondria ■ salts ■ sodium ■ T lymphocytes

WHITHER SODIUM?

Earlier, all was clear.[1] The intracellular composition (muscle for instance) exhibited a sodium concentration of ±10 mmol/L, potassium concentration of ±160 mmol/L, magnesium concentration of ±35 mmol/L, etc. Anions were protein and phosphate. In the extracellular plasma water, the corresponding concentrations were sodium, ±151 mmol/L and potassium, ±4.3 mmol/L. In humans, the electrolytes were distributed within the (about 40 L) total body water; two-thirds were inside cells and one-third outside cells. Sodium was mostly exchangeable and extracellular although some was deposited in bone, the fate of which was largely unclear but not so exchangeable. By the 1970s, the regulation of these constituents had been well worked out and balance concepts were sufficiently accepted to support pressure natriuresis of blood pressure regulation and our understanding of salt and water balance.[2] These ideas, and the supportive body of evidence, served us clinically well and were convincing. A veritable clinical tool was the knowledge generated by Edelman et al[3] and Birkenfeld et al.[4] They studied the relationship between plasma sodium, exchangeable sodium, exchangeable potassium, and total body water. Their insights showed us that by calculating effective free water clearance, we clinicians could always predict whose plasma sodium was going up or down and even at what rate the changes would occur. As a result, we had a fairly clear understanding of total body water, electrolyte contents, plasma concentrations, and subsequent speculations on blood pressure regulation. Osmotic forces, being what they are, would dictate that gain of exchangeable components would increase water and vice versa. That these ideas (a standard model if you will) could have immunologic implications never occurred to us, and we did not need anything else.

Standard models work until the mathematical infrastructure becomes wobbly. Titze et al[5] studied only 3 people but those for weeks over time, in a Mars-flight simulation study. The subjects resided in a capsule over

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Nonstandard Abbreviations and Acronyms

CVD	cardiovascular disease
EAE	experimental autoimmune encephalomyelitis
HSD	high-salt diet
IL	interleukin
NCLX	Na+/Ca2+ exchanger
Th17	T helper 17
VEGF-C	vascular endothelial growth factor C

weeks. The sodium and all components of the diet were known. The investigators' findings that sodium accumulation ran largely independent of water accumulation (or vice versa) was unexpected and stressed the standard model. How do we fit these findings into our understanding of human physiology?

The next task was to discover where the not-so-exchangeable sodium could be hiding. This experiment required carcass ashing and electrolyte measurements with atomic absorption spectroscopy.[6] The skin proved to be an osmotically inactive, sodium accumulation site, an area that was also influenced by extremes of dietary salt intake or kidney function. Humans carry around about 5 kg of skin, and skin is the largest reservoir of extracellular fluid in the body. Skin is particularly rich in glycosaminoglycans, which because of their strong negative charge, in particular for sulphated glycosaminoglycans, became a prime candidate for a sodium interaction. Support for a role of glycosaminoglycans, in particular, sulphated glycosaminoglycans, was found in initial studies.[7,8] However, this notion has been contested in 2 more recent rodent studies showing either no change or a reduction in glycosaminoglycans in animals receiving a high-salt diet (HSD) or in the deoxycorticosterone acetate and high-salt diet (DOCA)-salt model, respectively.[9,10] Moreover, no indication of Na^+ binding to glycosaminoglycans was identified.[10] Thus, follow-up studies have to address this issue and to explain the discrepancies. Does sodium accumulation apply to man?

The development of magnetic resonance imaging for sodium allowed to visualize and quantify the tissue sodium content in humans.[11] Of note, sodium content appeared to be higher in skin than in muscle for men, while women tended to have higher muscle sodium.[12] Interestingly, hypertensive patients, patients with end-stage renal disease, as well as patients with autoimmune disease display an increased sodium content in this third space.[13] Sodium stores seem to be dynamic, since SGLT-2 inhibition in patients with type 2 diabetes,[14] diuretic treatment in patients with acute heart failure,[15] successful treatment of patients with primary aldosteronism,[11] hemodialysis,[16] and after kidney transplantation[17] show reduced tissue sodium content. In addition, an experimental HSD study in humans triggered cutaneous Na^+ deposition as assessed by chemical analysis of punch biopsies.[18] These findings indicate that stored sodium can be mobilized. However, whether or not the sodium is readily exchangeable to immediately satisfy the Edelman equation is another issue.

These largely descriptive findings were enhanced by additional human balance studies in another Mars-simulation study. However, in this study, dietary salt intake could be manipulated. The subjects ingested diets differing only in 3 levels of sodium content. The investigators confirmed results from the earlier Mars-flight simulation study and found rhythmic sodium excretory and retention patterns that are independent of blood pressure or body water and occur independently of salt intake.[19] The idea that sodium can accumulate in skin and skeletal muscle is now generally accepted,[20,21] while how sodium influences blood pressure is not.[21] Taken together, these hosts of findings suggested that the standard model requires revision. More importantly, what local molecular mechanisms could help us further?

The answers lay in basic research. Parallel to the above reports, the Titze group focused on addressing the mechanisms involved. They were aware that TonEBP (tonicity-responsive enhancer-binding protein; NFAT5 [nuclear factor of activated T-cells 5])—a rel-like protein that activates transcription in response to hypertonicity—can detect even minimal changes in osmolarity.[22] HSD led to interstitial hypertonic sodium accumulation in skin, resulting in increased density and hyperplasia of the lymph-capillary network. Mechanistically, the NFAT5–VEGF-C (vascular endothelial growth factor C) axis in mononuclear phagocytes infiltrating the interstitium of the skin was the underlying mechanism for these effects on skin lymphatics. Mononuclear phagocyte depletion or VEGF-C trapping by soluble VEGFR-3 (vascular endothelial growth factor receptor-3) blocked VEGF-C signaling, augmented interstitial hypertonic volume retention, decreased endothelial NO synthase expression, and elevated blood pressure in response to HSD.[23] These preclinical findings were the first to connect immune cells with salt balance, which was also observed in humans in later follow-up studies.[24,25] Obvious calls were issued to confirm these results that were based on the uncomfortable assumption that differences in osmolality can exist between cell surfaces in a nanometer range. Thus, the experiments were repeated. The subsequent results demonstrated that the skin harbors a hypertonic fluid compartment in which mononuclear phagocytes modify local cutaneous electrolyte clearance via NFAT5 and VEGF-C/VEGFR-3–mediated modulation of cutaneous lymphatic capillary function. Thereby, mononuclear phagocytes carry out a homeostatic and blood pressure–regulatory function (Figure 1).[26] In this study, several confirmatory methods were used to investigate

the osmolar differences at the cellular level.[26,27] Subsequently, these ideas were translated to an infectious disease and inflammatory skin diseases, incorporating both magnetic resonance imaging for sodium and molecular data.[13,28–30] Most recently, a link between inflammation, metabolic dysfunction in obesity, and tissue sodium levels was established.[31] These ideas, particularly those concerning osmolar gradients in the nanometer range, understandably caused skepticism.[32] However, as discussed earlier, the methods available at the present time did not give sufficient detailed spatial information to allow resolving these questions. Methodological differences could be responsible. For instance, the precision ashing of tissues and atomic absorption spectroscopy (rats) to measure cation concentrations was not performed in all studies. These methods require expensive and not distributable facilities. Recent data from the Pravenec laboratory, which measured such precautions, supported the notion that sodium accumulation and blood capillary rarefaction in the skin predisposes to hypertension in a rat model.[27] Nonetheless, we argue that immune cells are involved in electrolyte metabolism, even at the most local of levels. We are convinced that this argument is compelling.

SODIUM SHIFTS THE IMMUNE CELL BALANCE TOWARD INFLAMMATION

Immune cells patrol throughout our body, change location from gut or bone marrow to the circulation, spleen, lymph nodes, and to target organs to fulfill their diverse functions. On their way, they sense and integrate diverse environmental signals, translate them into intracellular

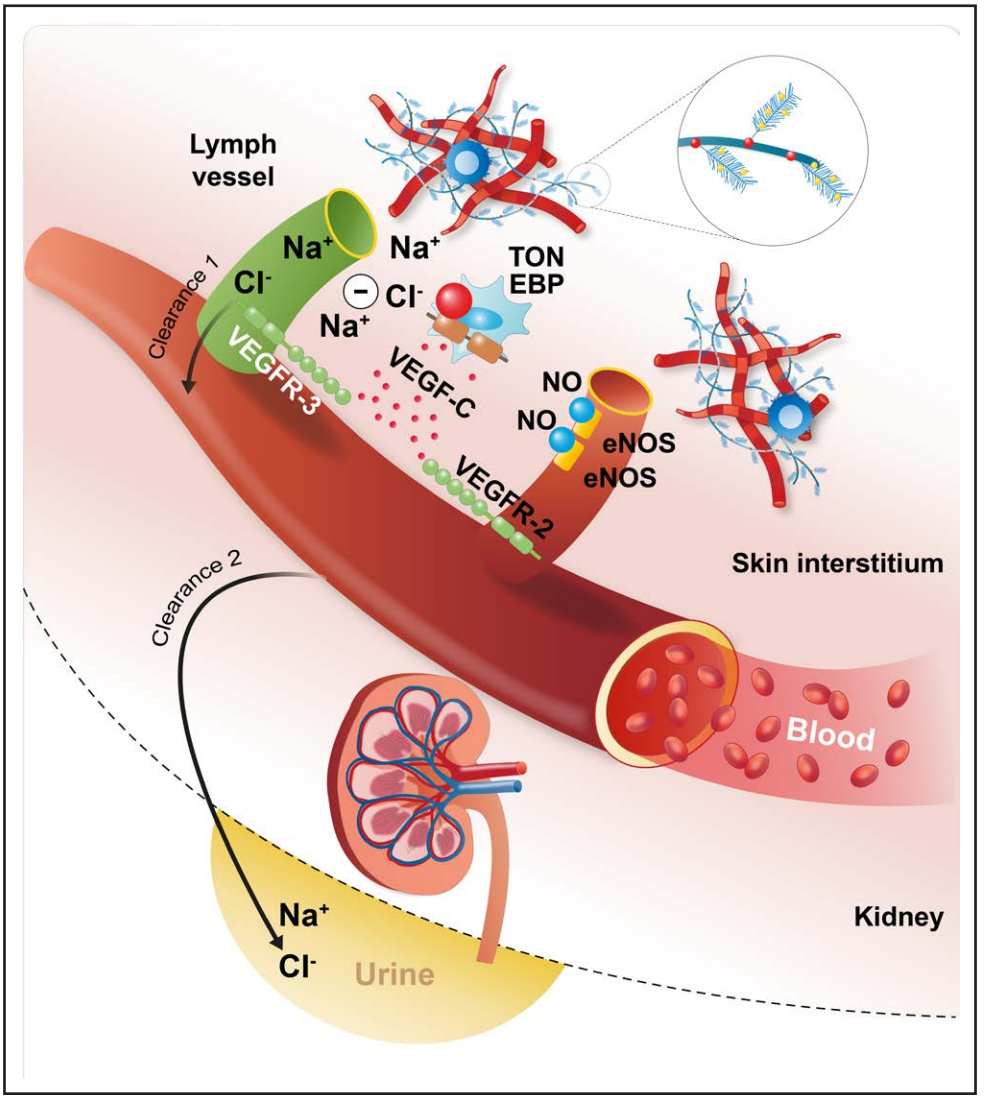

Figure 1. A schematic diagram of how local (nanometer domain) sodium gradients influence osmotic sensors, effectors, and immune cells.
eNOS indicates endothelial NO synthase; TonEBP, tonicity-responsive enhancer-binding protein; VEGF-C, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor-2; and VEGFR-3, vascular endothelial growth factor receptor-3.

information to permit adaption to a particular inflammatory environment for the maintenance of immune homeostasis. In the 1990s, investigators aimed to study the mechanism of saturated potassium iodide to treat infections. They used increases in NaCl as a control and found that increases by 40 mM, which is similar to increases found in skin stores upon dietary and inflammatory stimuli, could provoke proinflammatory responses in peripheral blood mononuclear cells.[33] These findings were among the first studies to show that ionic signals are able to profoundly impact immune cell responses. Since then, the literature clearly demonstrates that high-salt conditions favor proinflammatory macrophage and T helper 17 (Th17) cell activation and curtail the regulatory and anti-inflammatory activation of these cells.[34,35] In macrophages, the NCLX (Na^+/Ca^{2+} exchanger) is critically involved in sensing ionic sodium balance changes[36] and triggers enhanced activation of osmoprotective signaling pathways, such as NFAT5. Of utmost interest, these high salt responses contain profound metabolic adaption of macrophages, which includes triggering increased stabilization of hypoxia-inducible factor 1α and autophagy.[37] This process helps to fight infections.[27,36–40] Increased local sodium conditions, therefore, represent a local microenvironmental cue, which can strengthen barrier surfaces.[27,40,41]

In 2013, 2 landmark studies[42,43] connected high salt intake as a potential environmental factor contributing to experimental autoimmunity. These investigations showed that high NaCl conditions could boost the differentiation of naive $CD4^+$ T cells in humans and mice into pathogenic Th17 cells. IL (interleukin)-17A and IL-23R (IL-23 receptor) expression under Th17 differentiation conditions was enhanced. This regulatory mechanism involved p38/MAPK (mitogen-activated protein kinase), NFAT5, and SGK1.[34] SGK1 inactivates FOXO1 (forkhead box O1), thereby promoting enhanced RORγt (retinoic acid receptor-related orphan receptor gamma t) and IL-23R expression.[43] In vivo, an HSD increases the number of Th17 cells in gut-associated lymphoid tissue and the central nervous system, resulting in exacerbating experimental autoimmune encephalomyelitis (EAE), a mouse model mimicking many aspects of multiple sclerosis.[42,43] $CD4^+$ T cell–specific SGK1 (serum/glucocorticoid regulated kinase 1) deletion in mice leads to resistance to EAE, owing to a defect in maintaining the Th17 phenotype.[43] Both in vitro and in vivo evidence in EAE suggests that Th17 activation by high NaCl is not mediated through dendritic cells but rather through a separate pathway or direct impact on Th17 cells.[44] Besides the NFAT5 axis, high salt also affects SGK1 via the upstream long noncoding RNA (Lnc)-SGK1.[45] Furthermore, aside from its pivotal role in T cells, SGK1 in dendritic cells is important for salt-sensitive hypertension, vascular function, and renal inflammation.[46] Translating these experimental findings to humans, a 10-day HSD (15 g NaCl/day, about 300 mmol Na^+/day) in healthy nonsmoking male volunteers resulted in increased Th17 population in the peripheral blood, which was reversed after switching the men to normal-salt diet.[47] Further, also a rather moderate 14-day dietary high-salt challenge (6 g of NaCl/day in addition to accustomed diets) increased circulating Th17 frequencies.[48] Of note, in humans, potassium also affects high salt–induced Th17 polarization by a thus far unknown mechanism.[49] Circulating IL-17 levels were significantly increased after switching from 3 to 18 g of NaCl for 7 days, while the addition of 4.5 g KCl to the HSD completely reversed the IL-17 levels.[49] A dichotomous role for NaCl on Th17-like cells has also been reported, where the impact of NaCl on $CD4^+$ T cells may be context dependent and could differ depending on stimulation and cytokine environment.[50]

IL-17 plays a critical role in infections, autoimmune diseases, and inflammatory diseases. Of note, hypertensive humans show significantly increased circulating IL-17 levels.[51] Physiologically, IL-17 is not only involved in host defense but also may promote inflammatory tissue damage. IL-17A knockout mice initially increase the blood pressure similarly to controls upon angiotensin II infusion, whereas over time, they develop a less hypertensive state.[51] In addition, human prototype IL-17–related diseases such as psoriasis, periodontal disease, and rheumatoid arthritis are also associated with hypertension.[52–54]

High salt is further linked to an increased risk of cerebrovascular diseases and dementia. A recent study focusing on the gut-brain axis described how high salt initiates a Th17 response in the gut resulting in a marked increase in plasma IL-17, which subsequently suppresses resting cerebral blood flow and endothelial function, leading to neurovascular dysregulation and cognitive impairment.[55] Endothelial dysfunction and cognitive impairment are mediated via inhibitory Rho kinase–dependent phosphorylation of endothelial NO synthase with reduced NO production of cerebral endothelial cells.[55]

Lupus-prone MRL/lpr mice under HSD showed a significant increase in the ratio of splenic Th1/Th2 and Th17/Regulatory T (Treg) cells, accompanied with reduced survival.[56,57] In BALB/c mice, HSD induced tubular proteinuria and a profibrotic phenotype with increased renal cortical Th1 and Th17 and reduced Treg cells.[58] HSD also primed follicular helper T-cell differentiation and promoted autoimmunity by hydroxytransferase TET2 (Ten-Eleven Translocation 2)-induced DNA demethylation. In vitro, TET2 silencing reduced NaCl-induced follicular helper T-cell polarization. In models of colitis, several reports have established the relationship between high sodium and Th17 cells. In human intestinal lamina propria mononuclear cells, IL-17A, IL-23R, TNF-α, and RORγt significantly increased after NaCl exposure.[59] Mice on HSD developed severe 2,4,6-trinitrobenzenesulfonic acid (TNBS)- or dextran sulfate

sodium (DSS)-induced colitis compared with control mice, which could be ameliorated by p38 MAPK inhibition.[59] Besides Th17 cells, IL-17–producing type 3 innate lymphoid cells may also be affected by HSD in this context. When mice were fed an HSD, an intestinal inflammatory response associated with increased IL-23 production, neutrophil mobilization, and frequency of IL-17–producing type 3 innate lymphoid cells in the colon was observed. Since intestinal inflammation was not observed in IL-17 knockout mice but albeit to a lesser degree in recombination-activating genes (RAG)-deficient mice, which lack B and T cells but have ILC, IL-17 production by both type 3 innate lymphoid cells and Th17 cells likely contributes to the inflammatory response.[60] Altogether, these data suggest that a high salt intake may prime various T-cell subsets, promote IL-17 production with consequences for the pathogenesis of cardiovascular diseases (CVDs) and autoimmune diseases. Whether or not reducing salt intake to currently recommended levels would reduce this state of affairs remains to be seen.

SODIUM AFFECTS THE MICROBIOME AND INTESTINAL INFLAMMATION

Recent research has further been focusing on indirect roles of NaCl regulating immunity through changing the gut microbiota.[34] High salt intake impacts the gut microbiota in mice and humans, particularly by depleting *Lactobacillus* spp.[48,61–63] Along with changes in the gut microbiota, HSD increases the frequency of Th17 cells in the intestines, spleen, and spinal cord along with the blood pressure and aggravated disease courses of EAE mice.[48] Replenishment of live *Lactobacillus murinus* to HSD-fed mice ameliorated the HSD-mediated exacerbation of EAE and salt-sensitive hypertension by regulating Th17 cells, likely through increased levels of the bacterial tryptophan metabolite indole-3 lactic acid. Mechanistically, indole-3 lactic acid suppressed Th17 cell polarization, suggesting that tryptophan metabolites of bacterial origin may act as inhibitors of the high salt–induced Th17 increase of the host.[48] Concordantly, a meta-analysis demonstrated that probiotics (mostly containing *Lactobacillus* spp.) may reduce blood pressure in hypertensive subjects.[64] Kirabo et al[65] also have shown that a high salt intake is associated with changes in the gut microbiome, as well as higher blood pressures in humans. Further, blood pressures in salt-treated mice were elevated when the mice received subpressor doses of Ang II (angiotensin II).[65] HSD was associated with changes in an increase in the genera *Firmicutes*, *Proteobacteria*, and *Prevotella* bacteria and a decrease in the genera of lactic acid–producing bacteria.[65] Adaptive fecal microbial transfer from mice fed an HSD predisposes germ-free recipients to inflammation and hypertension.[65] Further evidence for microbiota-dependent effects of an HSD on inflammation is the observation that an HSD promotes experimental DSS- and dinitrobenzenesulfonic acid–induced colitis in mice by reducing the presence of intestinal *Lactobacilli* and butyrate production. This effect was not observed in germ-free mice.[62]

SODIUM BLUNTS ANTI-INFLAMMATORY REGULATORY T-CELL FUNCTION

Regulatory FOXP3$^+$ (forkhead box P3) T cells (Tregs) play an essential role for the maintenance of peripheral tolerance and immune cell homeostasis.[66,67] Depending on the microenvironment and tissue, Tregs show the ability to suppress innate and adaptive immune cells by the secretion of anti-inflammatory cytokines, such as IL-10, or by cell-cell contact-dependent mechanism involving costimulatory receptors like cytotoxic T-lymphocyte–associated protein 4.[66,67] In humans, mutations in the *FOXP3* gene, a master regulator of Tregs, lead to dysfunctional Tregs with fatal autoimmunity. Mutations have been linked to multiple sclerosis, type 1 diabetes, systemic lupus erythematosus, chronic infections, or inflammation like rheumatoid arthritis.[66–69] Further, differential expression of *FOXP3* splice variants related to Treg function was associated with unstable plaques in patients with atherosclerosis.[70] Experimental and clinical studies confirmed that Tregs are important mediators to contain chronic inflammation in CVD such as atherosclerosis,[71] hypertensive target organ damage,[72] or wound healing after myocardial infarction.[73] However, importantly, reduced Treg numbers and a dysfunctional Treg phenotype similar to autoimmunity have been reported in atherosclerosis, heart failure, and myocardial infarction and are associated with progression of disease.[74–77] Furthermore, HSD also negatively affected the regulatory balance of T cells in transplantation and precipitates rejection.[78] Of note, the deleterious effect of an HSD in the absence of SGK1 on CD4$^+$ T cells in transplanted recipients was diminished.[78]

Mechanistically, dysfunctional Tregs found in several inflammatory diseases are characterized by a proinflammatory Th1-like phenotype with high expression levels of IFN-γ (interferon-γ) and lower levels of IL-10.[66,79–81] Several reports suggested that SGK1 not only plays a pivotal role in high salt–induced Th17 cell polarization[29,42,43] but also in Tregs.[50,78,79,82–84] In vitro and in vivo, salt-SGK1 signaling axis enables Treg cells to acquire a Th17-like phenotype, thus establishing salt as a nonimmune factor that affects Treg functional adaptation.[85] In vitro, high salt was sufficient to induce RORγt expression in both thymic Treg and inducible Tregs without IL-17A production.[85] A moderate decrease in FOXP3 expression in thymic high salt–induced RORγt$^+$ Treg cells was not associated with a loss of Treg identity and function most likely due to still sufficient FOXP3 levels. In contrast, IL-23[84] or IL-1β[86] can readily induce IL-17A$^+$RORgt$^+$FOXP3$^+$ inducible Treg cells into inflammatory Th17-like Treg cells. These data suggest that salt-induced Treg dysfunction could

accelerate not only the pathogenesis of autoimmune disease but also the progression of CVD.

SODIUM INHIBITS MITOCHONDRIAL FUNCTION

As mentioned above, sodium is the most abundant cation in the extracellular space, kept in low concentrations intracellularly. This asymmetrical distribution builds up a high electrochemical gradient across the plasma membrane and allows for a fast and substantial sodium influx. The latter is mediated by different channels and transporters, such as the NHE (sodium-proton exchanger), the NKCC (sodium-potassium-chloride cotransporter), the NCLX, the TRPM4 (transient receptor potential melastatin 4), and the amiloride-sensitive sodium channel.[87] Sodium influx and efflux not only affect cell membrane potential, excitation, and electrochemical conductivity but also intracellular pH and concentration of other ions and metabolites.

Interestingly, during ischemia, sodium not only accumulates in myocardial tissue but was also shown to invade the intracellular space and accumulate in subcellular compartments, more concretely, in the mitochondria. The contraction of healthy cardiac myocytes consumes large quantities of ATP, which is produced by mitochondrial oxidative phosphorylation.[88] During cardiac ischemia, intracellular and mitochondrial Na^+ levels increase along with a reduction in mitochondrial respiration with reduced ATP production (Figure 2), which might, in part, explain the imbalance of the energy demand in the failing heart.[88] Also studies in patients with type 2 diabetes have shown that the myocardium under these conditions display reduced mitochondrial respiration and higher oxidative stress, further linking mitochondrial dysfunction with the pathophysiology of heart failure.[89] Besides its effect on oxidative phosphorylation, the Na^+ overload can cause an imbalance in Ca^{2+} homeostasis by reverting the calcium-sodium exchange process and thus accelerate heart failure.[90,91] These studies highlight how HSD and imbalances in the ionic microenvironment can be detrimental to a plethora of different diseases and how cellular metabolic shifts are key in regulating cellular function and overall homeostasis.

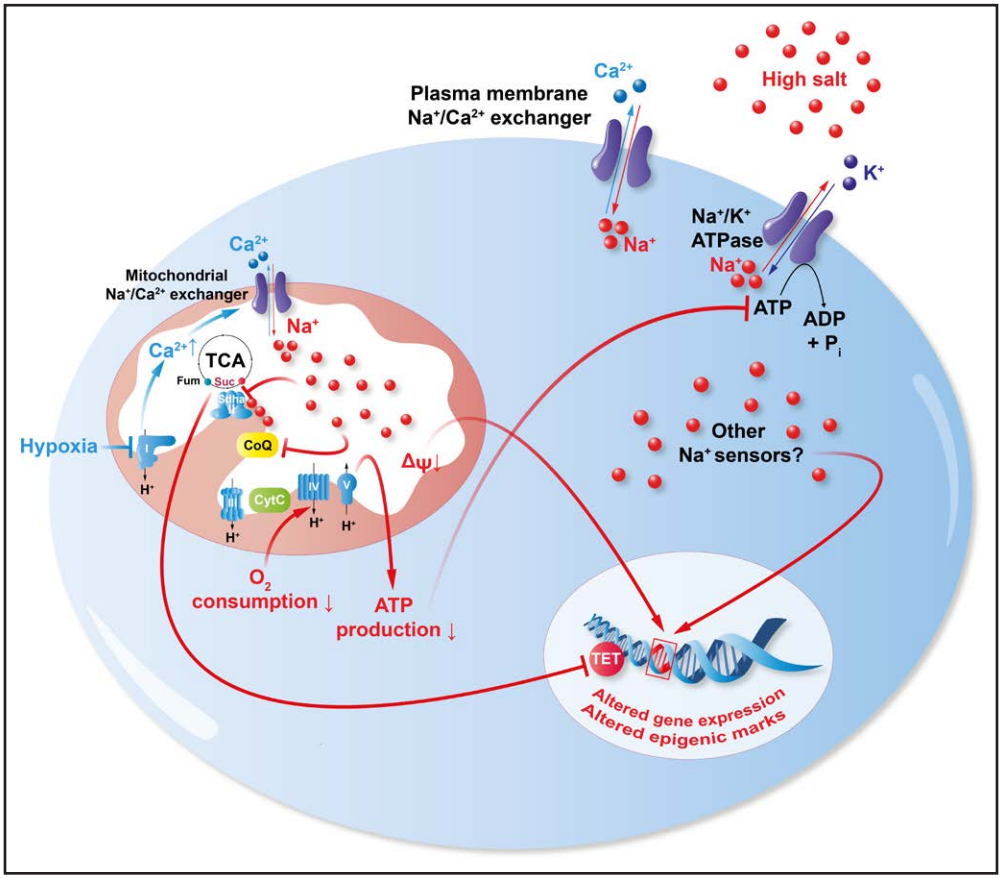

Figure 2. Sodium and mitochondrial metabolism.
Pictogram of a cell under hypoxic or hypertonic saline conditions. Sodium enters the cell and mitochondria (at least, in part) via the NCLX (Na^+/Ca^{2+} exchanger) and inhibits the electron transfer chain at the level of succinate dehydrogenase complex flavoprotein subunit A complex II (Sdha, II)/ubiquinone (CoQ). Subsequently, mitochondrial respiration, membrane potential ($\Delta\Psi$), and ATP production are reduced. In several immune cells, a proinflammatory gene expression is observed. CytC indicates cytochomre C; Fum, fumarate; Suc, succinate; TCA, tricarboxylic acid cycle; and TET, ten-eleven translocation.

It was shown that sodium could impact circulating and tissue-invading monocytes, M1/M2 macrophages, dendritic cells,[87] and as outlined before in detail, Th17 cells and Tregs, as well as vascular endothelial cell stiffness.[34] Interestingly, many of these phenotypes are mediated by NCLX, both at the plasma and the inner mitochondrial membrane. With these findings, there has been a strong focus on how sodium affects cellular bioenergetics.

Cellular metabolism and specifically its plasticity are undoubtedly of outmost importance for cell function and adaptation. Metabolic reprogramming is not just a hallmark of cancer but also emerged as critical regulator of immune cell activation.[92,93] Sodium was shown to have several metabolic targets. In ischemic myocardial tissue, mononuclear phagocytes, and Tregs, sodium reduces mitochondrial oxidative phosphorylation. Sodium could enter the mitochondrial matrix via NCLX and interacts with phospholipids in the inner mitochondrial membrane, reducing the membrane fluidity and the diffusion of ubiquinone between complex II and complex III of the electron transport chain.[94] In M1/M2 macrophages[38] and Tregs,[95] salt directly inhibits complex II/III of the electron transport chain. Treg cell–specific ablation of mitochondrial respiratory chain complex III in mice resulted in loss of function and subsequent development of fatal inflammatory disease early in life, without altering Treg cell proliferation and survival.[96] Recent data demonstrated that high salt mirrored the metabolic and gene expression signatures and functional phenotype observed after complex III inhibition.[95] The loss of mitochondrial function after short-term engagement in high-salt environments in vitro provoked a long-term loss of function of human and murine Tregs in vivo.[95] Xenogeneic graft versus host disease in immunodeficient mice is a model for in vivo analysis of human Treg functionality.[83,97,98] Adoptive transfer of high salt–treated or complex III inhibited human Tregs in xenogeneic graft versus host disease or murine high salt–treated Tregs to EAE similarly have long-term consequences in vivo.[95] Interestingly, inhibition of CII/III is accompanied by an accumulation of succinate, which in turn inhibits TET2-mediated DNA demethylation (Figure 2). This accumulation could be a potential mechanism by which HSD induces altered epigenetic markers and thereby produces long-term effects despite a relatively short-term high-salt stimulation. Besides electron transport chain complex II/III, in cancer and macrophage cell lines, salt induces aerobic glycolysis via a pyruvate dehydrogenase kinase–mediated activation of pyruvate dehydrogenase, with reduced tricarboxylic acid cycling and oxidative phosphorylation. Interestingly, sodium was recently also identified as a regulator of the liquidity of intracellular condensates, affecting protein-protein interactions (at least partially by electrostatic shielding of the proteins) and thus protein aggregation under hypertonic stress.[99] However, the exact extend of salt-induced metabolic remodeling in various different cell types remains ill defined. And there are so far only limited data available in respect to time resolution of salt-induced metabolic remodeling in different cell types under different metabolic states. The integration and investigation of in-parallel–occurring signaling events will be crucial to understand these processes in more detail.

OUTLOOK

Accumulating evidence suggests that the blood pressure–centric definition of salt sensitivity could be broadened to cellular and metabolic sodium sensitivity. While the actions of other cations such as Ca^{2+} as important intracellular messengers are widely recognized, evidence continues to accumulate highlighting various unexpected roles of sodium in the regulation of cellular function. Overall, it is becoming clearer that sodium modulates broader bodily functions besides fluid homeostasis and regulates various cell functions, particularly in cells of the innate and adaptive immune system. Given the relevance of immune function for CVD and cardiometabolic disease, it is tempting to speculate that these findings may have important implications and are not only relevant for autoimmunity. However, it remains elusive as to where, why, and how sodium is compartmentalized, both on a tissue/supracellular and organelle/subcellular level and whether all cells are similarly sodium responsive. More research is needed to understand how tissue or cellular salinization is linked to health or disease states, age, and gender, as well as nutrition, and how metabolic plasticity on both the cellular and body level is affected.

Recent investigations (and studies well back in the 20th century) showed that the substitution of Na^+ with K^+ (in terms of intake) showed significantly lower rates of stroke, major adverse cardiovascular events, and death from any cause.[100] The driving force for this potassium-protection idea were the seminal studies and observations from the Tobian group.[101] With potassium augmentation, better systolic blood pressure lowering was observed,[102] compared with those subjects who received a regular salt intake. Whether or not salt (NaCl) reduction or salt substitution by KCl can affect the tissue/supracellular and organelle/subcellular micromilieu, signaling, and immunometabolism should be addressed in future studies. By understanding the dependencies for these microenvironmental changes and the corresponding environmental sensing mechanisms, we envision targeted approaches to fine-tune immune cell, myocardial, fibroblast, and endothelial cell function and thus better control inflammation and CVD.

ARTICLE INFORMATION

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