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SKIN LYMPHATIC SYSTEM IN THE PATHOGENESIS OF ARTERIAL HYPERTENSION – REVIEW AND CRITIQUE

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ABSTRACT

Although numerous studies have confirmed the relationship between high salt intake and elevated blood pressure, the exact molecular mechanisms of this relationship are still unclear. There is growing evidence that skin interstitium, as well as the skin lymphatic system, are important regulators of both sodium (Na+) balance and blood pressure. Skin is in itself a large reservoir of Na+ ions which are stored in an osmotically inactive form on glycosaminoglycans (GAGs). Local hypertonicity due to extensive accumulation of Na+ within the skin as a result of a high-salt diet was demonstrated to induce macrophages to express a transcription factor termed tonicity-responsive enhancer binding protein (TonEBP) and subsequently to secrete vascular endothelial growth factor-C (VEGF-C), activating lymphangiogenesis within the skin. This regulatory axis seems to be adaptive in maintaining blood pressure in high salt-load states. Recent studies have added new insights into the functioning of lymphatic vessels and the pathogenesis of salt-sensitive hypertension as well as questioned the classic view of Na+ homeostasis. This review aims to summarize recent findings pertaining to the involvement of the skin lymphatic system in Na+ and blood pressure regulation.

Keywords: arterial hypertension, skin lymphatics, lymphangiogenesis, sodium, salt sensitivity, glycosaminoglycans (GAGs), tonicity-responsive enhancer binding protein (TonEBP), vascular endothelial growth factor-C (VEGF-C)

The skin is the largest and complex organ in humans and is made up of two layers (1). The most superficial layer, the epidermis, is avascular. The deeper skin dermis however contains a widely distributed network of both blood and lymphatic vessels. Lymphatic capillaries within the skin originate as the blind-ending initial lymphatics, which begin to converge and coalesce, forming progressively larger collecting lymphatic vessels (2). The skin lymphatic system can be subdivided into superficial and deep lymphatic plexuses. The superficial plexus is formed only by the lymphatic capillary network, whereas the deep lymphatic plexus contains also collecting lymphatic vessels (3) (*Fig.1*).

The primary function of the lymphatic system is the maintenance of fluid homeostasis within tissues by providing a route for the return of the extravasated interstitial fluid into the bloodstream. The lymphatic system is also a component of the immune system. Impairment of the dermal lymphatic system results in edema as well as recurrent skin infections (2). Several recent studies have highlighted that the lymphatic system plays an important role in the pathophysiology of various cardiovascular and metabolic diseases, including atherosclerosis, insulin resistance, diabetes, and obesity (4,5). There is also increasing evidence that lymphatic vessels in the skin are crucial in the pathogenesis of salt-sensitive hypertension.

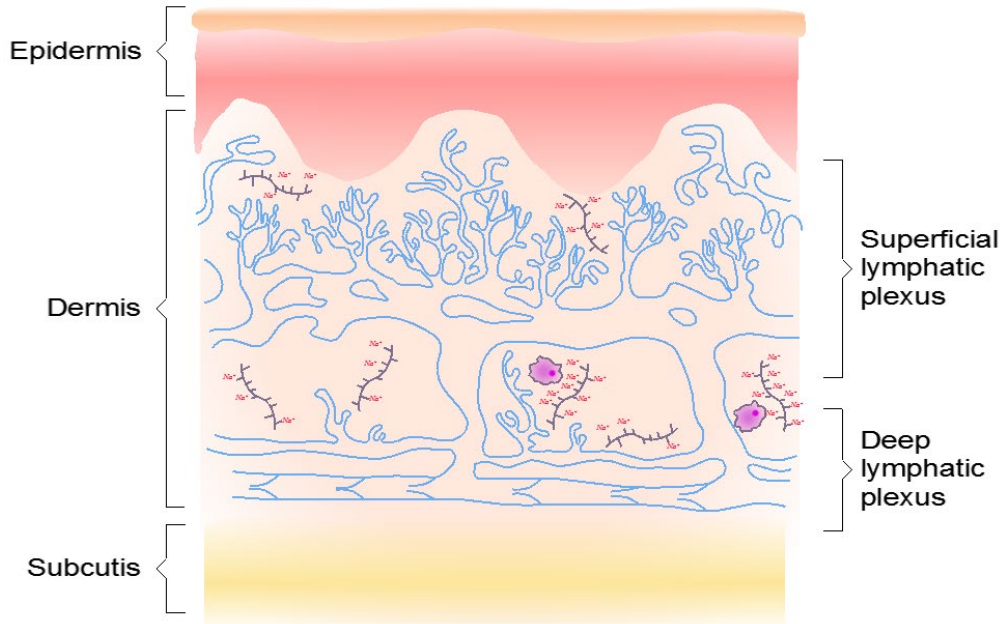

Fig. 1. Schematic of lymphatic vessels, glycosaminoglycans and macrophages in the skin.

The concept that arterial hypertension might result from lymphatic system dysfunction was hypothesized for the first time in 1998 (6). To date, the direct relationship between salt-sensitive hypertension and the skin lymphatic system has been demonstrated mainly within the rodent model (7,8), and many questions still remain unanswered. New discoveries continue to change our traditional understanding of both skin interstitium functioning and Na+ and fluid homeostasis and have opened a new door for future investigations.

Salt Sensitivity

Numerous clinical and experimental studies have demonstrated that a high-salt diet is associated with the development of hypertension (9-12). Current guidelines recommend reduction of salt intake to 5g/day in the general population, and this recommendation is seen as one of the most important steps in the non-pharmacological management of hypertension (13). However, recent data from the PURE study suggests that salt reduction below a certain level (<3g/day) may be harmful and the optimal daily intake of salt should be between 4-6g/day (14,15).

Generally, salt sensitivity is defined as a susceptibility to demonstrate a significant increase in blood pressure following salt loading and a decrease in blood pressure following a reduction in salt intake. Conversely, salt resistance means that blood pressure does not change or may even fall after salt supplementation (9,16,17). Salt-sensitivity occurs in 50% of patients with hypertension in the Caucasian race and in 75% of hypertensives among Afro-Americans (18-21). This trait is not only limited to the hypertensive group but also occurs in normotensives (approximately in 20%) (20,21). It becomes more prevalent in older age (16,17), renal dysfunction (22), obesity, and diabetes mellitus (23). It leads to the development of hypertension and is associated with a worse prognosis (24). When survival curves were examined, normotensive salt-sensitive subjects were found to have cumulative mortality similar to that of hypertensive subjects (24).

The precise molecular mechanisms

underlying the effects of excessive dietary Na+ on high blood pressure are still not clear and many different hypotheses have been proposed. Recent findings suggest that salt sensitivity is associated with vascular dysfunction manifested by the inability of blood vessels to vasodilate in response to salt loading (25). It has also been demonstrated that excessive Na+ intake causes severe damage to the endothelial glycocalyx, which then enables Na+ entry into the endothelial cells and results in endothelial dysfunction (26). Other plausible explanations of vascular dysfunction from salt sensitivity relate to the possible inhibition of vasodilation by asymmetrical dimethylarginine (ADMA), the levels of which are abnormally increased by Na+ (27). Another proposed explanation of salt sensitivity pertains to a possible interaction between the immune system and the vasculature, resulting in an inflammatory state at sites of excessive accumulation of Na+ (25,28,29). In line with these studies is the finding that a high-salt diet significantly increases hormonal vasoreactivity of pre-capillary resistance arterioles in the skin toward angiotensin-2 and noradrenaline, and this way could increase peripheral resistance and contribute to higher blood pressure in salt-sensitive hypertension (30).

Three-Compartment Model of Sodium Balance

Numerous sodium balance studies have indicated that exposure to a high-salt diet can lead to Na+ retention as the excessive Na+ load is not completely excreted by the kidneys but accumulates without commensurate water retention elsewhere in the body (three-compartments model of sodium balance) (31-34). Interestingly, human spaceflight studies have further supported this osmotically inactive Na+ storage mechanism (35). Long-term observations in subjects with a constant Na+ intake have shown large fluctuations in diurnal Na+ excretion, with no correlation between Na+ intake and excretion. There was however a correlation between Na+ excretion and aldosterone or cortisol secretion, and these correlations were independent of blood pressure value or body water content (36).

Sodium and Glycosaminoglycans in the Skin Interstitium

Ivanova et al as early as in 1978 demonstrated that Na+ can accumulate within the skin of rats and that under conditions of high Na+ intake the concentration of skin Na+ increases. It was suggested that the mechanism behind this accumulation of Na+ was an increase in Na+ binding to sulphated glycosaminoglycans (GAGs) within the skin (37,38). Further experiments on the rodent model performed by Titze and collaborators confirmed that large amounts of Na+ are stored in the skin (39-42). In the study of Heer et al, Na+ retention in the skin was also confirmed to exist in healthy men (32). We examined Na+ concentrations within abdominal skin specimens taken during elective surgery in patients both in hypertensive and control groups. Although we demonstrated that Na+ storage is present in human skin, we found no statistical difference in skin Na+ concentrations between the study groups. Moreover, we observed that increased Na+ content was associated with higher water retention (43). Studies with ^{23}Na magnetic resonance imaging (^{23}Na-MRI) enable quantitative visualization of Na+ content within the body (44). ^{23}Na-MRI studies have shown that Na+ storage in humans occurs primarily within the skin and skeletal muscle without concomitant water retention (45). ^{23}Na-MRI also revealed that Na+ content within the skin increases with age (45,46), is higher in men (45), in hypertension (45), and in other conditions which are known to be associated with salt sensitivity, including type 2 diabetes (47) and in hemodialysis patients (46).

Titze et al also reported that Na+ is stored within the skin of rodents in an osmotically inactive form attached to interstitial GAGs (7,39). GAGs are linear polysaccharide chains which possess a significant negative charge density (48) and have been shown to respond to increased dermal Na+ content by further increasing their charge density through increased polymerization and sulfonation (7,32,39). Conversely, long-term salt deprivation in rats appears to result in the

mobilization of osmotically inactive dermal Na+ from GAGs, and the concentration of GAGs decreases (49). A recent study in mice demonstrated that defective heparin sulfate polymerization leads to a decrease in Na+ and water content within the skin as well as to a higher heart rate, increased fluid intake, increased plasma osmolality, and to an abnormal response to Na+ loading (50). These strongly support the theory that GAGs within the dermal interstitium enable the skin to manage bound Na+ stores and to regulate water homeostasis (50).

Macrophages - TonEBP - VEGF-C - Lymphangiogenesis Axis in Salt-Sensitive Hypertension

Machnik et al demonstrated that rats fed a high-salt diet develop an increase in tonicity and osmotic stress within the dermal interstitium due to extensive skin Na+ storage. Hypertonic electrolyte accumulation within the skin promotes the infiltration of the mononuclear phagocyte system (MPS) cells (7,8). Macrophages are mobile osmosensors which actively move to the sites of higher salt concentration in the skin. Chemotaxis toward sites with higher salt concentration has been shown to be a macrophage-specific process although the exact molecular mechanism requires further investigation (51).

It has also been shown that MPS cells express a transcription factor termed tonicity-responsive enhancer binding protein (TonEBP, also known as nuclear factor of activated T cells 5, NFAT5), which subsequently increases the secretion of vascular endothelial growth factor C (VEGF-C), a known major lymphangiogenic growth factor. VEGF-C secreted by MPS cells acts via the VEGF receptor (VEGFR)-3 and stimulates lymphangiogenesis and increases lymphatic vessel density within the skin (8). VEGF-C also induces endothelial nitric oxide synthase (eNOS) expression (52). The impact of VEGF-C on lymphatic capillary vessels in the skin of rats on high-salt diet was manifest by both increased lymphatic capillary quantity as well as an increase in lymphatic capillary diameter, reflecting both lymphangiogenesis as well as hyperplasia of the preexisting lymph capillary network in response to dietary salt loading (8). Further studies have confirmed the functional nature of newly formed lymphatics induced by salt accumulation within the skin (53,54).

Inhibition of the TonEBP - VEGF-C - VEGFR3 axis in mice may be accomplished through genetic deletion of the TonEBP gene in MPS cells, by selective pharmacological blockade of the VEGFR3 receptor with an antibody, or by skin-specific trapping of VEGF-C in the skin. It results in the prevention of lymphangiogenesis, accumulation of electrolytes within the skin, and in elevated blood pressure (8). Similarly, macrophage depletion or inhibition of VEGF-C signaling within the skin of rats fed a high-salt diet promotes or aggravates salt-sensitive hypertension (55). These findings confirm that the lymphatic system likely plays an important role in the regulation of blood pressure and are in agreement with the clinical observations that hemangiogenesis/lymphangiogenesis inhibitors, which block VEGF signaling pathways and which are used in anticancer therapy, often result in hypertension (56,57).

The increased number and volume of dermal lymphatic capillaries resulting from continued lymphangiogenesis, may represent an adaptive mechanism that allows for a more effective form of removal of both Na+ and water from the skin interstitium (8,55). According to this view, the lymphatic system probably ensures that any Na+ stored within the skin is able to return to the blood circulation and then be excreted mainly via the urine. A high-salt diet has been demonstrated to enhance skin and muscle lymph flow by up to 26% and by 20%, respectively, as well as to increase the frequency of lymphatic vessel contractions (53). A high-salt diet has also been shown to differentially modulate the mechanical activity of afferent and efferent collecting lymphatics in murine iliac lymph nodes (58). These studies indicate that the lymphatic system adjusts its structure and activity to the quantity of Na+ within the skin. The osmolality and electrolyte concentration in lymph draining skin are equal in rats fed a

high-salt diet in comparison to rats fed a low-salt diet (59), suggesting that the clearance of osmolytes and electrolytes from tissues occurs via enhanced fluid clearance (53). This suggestion points to the importance of lymph flow as an integrated element of electrolyte homeostasis (53). Na+ removal from the skin might decrease the influence of Na+ accumulation on blood vessel constriction and, as a consequence, might lower blood pressure (30). Increased skin VEGF-C upregulates eNOS and NO production resulting in vasodilation. This mechanism may also directly contribute to blood pressure reduction (52) as it has been demonstrated that dermal vasculature contains biologically significant stores of NO which has the potential to influence systemic blood pressure (60).

VEGF-C and Salt-Sensitive Hypertension

The role of VEGF-C does not appear to be limited to its being the main mediator of lymphangiogenesis as well as an inductor of eNOS expression (7,8). It was also been shown that VEGF-C demonstrates a potential effect on the contractility of lymphatic collectors in the skin with higher Na+ concentrations, probably through VEGFR-3 (61). VEGF-C promotes the synthesis of hyaluronic acid resulting in a higher charge density of synthesized GAGs within the endothelial glycocalyx (62). Thus, it is possible that VEGF-C could also affect the actual structure of the GAGs within the skin, but this will require further investigation.

Concentrations of serum VEGF-C in hypertensive patients compared to control groups have been inconsistent in different studies – in some studies showing higher concentrations (8) while others, including our study, demonstrated lower concentrations (43,46). The concentration of circulating VEGF-C however appears to decrease with age (46). Interestingly, Na+ content within the skin increases with age. Thus, it has been suggested that the lower levels of VEGF-C in older age could be associated with lower Na+ clearance and could, therefore, lead to both a greater Na+ accumulation within the skin as well as potential arterial hypertension (46). Furthermore, dialysis patients with higher VEGF-C levels have been shown to be significantly better at Na+ clearance from the skin reservoirs during hemodialysis treatment (46). It has also been demonstrated that VEGF-C concentrations were higher during a high-salt diet than during a low-salt diet in patients with chronic kidney disease, whereas in healthy subjects this relationship was not statistically relevant (63,64). The concentra-tion of circulating VEGF-C might, therefore, be the marker of salt-sensitivity, as it has been demonstrated that circulating VEGF-C increases during a high-salt diet in salt-sensitive, but not salt-resistant, subjects (64).

Immune System and Lymphatic Vessels in Salt-sensitive Hypertension

Osmotic stress MPS cells infiltrate the skin interstitium in response to osmotic stress, with the induction of the TonEBP - VEGF-C - VEGFR3 regulatory axis, but without concomitant TNF λ (tumor necrosis factor λ) gene or protein expression (55). It has, therefore, been suggested that lymphangiogenesis in the skin, as a result of an excessive storage of Na+ within the skin, proceeds without a concomitant inflammatory response component (55). Nevertheless, there is growing evidence that the relationship between skin Na+ storage, the immune system, lymphatic vessels, and hypertension is strong and complex (65,66).

Chronic inflammation stimulates lymphangiogenesis (67). The role of T lymphocytes in the pathogenesis of salt-sensitive hypertension has been recently well established (68,69). Salt has been shown to promote the differentiation of CD4+ T cells into a Th-17 pro-inflammatory phenotype, which results in vascular dysfunction (70). Moreover, recent studies suggest that dendritic cells (DCs), which migrate from the skin to skin-draining lymph nodes, also may have a role in lymphangiogenesis within the skin interstitium. Such an assumption was based on the observation that although DCs within lymph nodes in the non-inflammatory steady-state mostly do not originate from upstream

tissue DCs, after an inflammatory stimulus, lymph-migrating tissue-derived DCs make up the majority of lymph node DCs (71). Further studies are needed to determine the exact role of dermal DCs in the process of lymphangiogenesis and Na+ homeostasis (65).

More studies are also necessary to determine the exact mechanisms regarding the participation of macrophages in the pathophysiology of hypertension. Although the role of macrophages in the skin seems to be protec-tive against salt-sensitive hypertension as macrophage depletion results in salt-sensitive hypertension in rats fed a high-salt diet (55), subsequent studies have suggested far more complex mechanisms concerning macrophages that need to be further clarified. Firstly, macrophages are highly heterogeneous immune cells and exhibit two different activation states – M1 (pro-inflammatory) and M2 (anti-inflammatory) (72). It has been demonstrated in rats that hypertension is associated with the M1 phenotype of macrophage and not with M2 (73). Moreover, it has also been revealed that, in the presence of non-inflammatory signals (e.g., IL-4 and IL-13), salt reduces macrophage activation while, conversely, salt appears to augment macrophage activation in a pro-inflammatory environment (e.g., lipopolysaccharide, LPS). This suggests that salt does not have one definite impact on macrophages but is modulated by other stimuli (74,75).

Regulation of Na+ Accumulation in the Skin Interstitium

The molecular mechanisms of Na+ entering the skin interstitium and its subsequent mobilization from interstitial tissue are still largely unknown. Studies with the use of ^{23}Na MRI have demonstrated that dialysis (46), spironolactone (46) and dapagliflozin (76) can mobilize Na+ from both the skin and muscle in humans and have the potential to decrease tissue content of Na+.

Recent findings also suggest that there is a local electrolyte gradient in the skin interstitium and that the skin creates its own electrolyte microenvironment. In the study of Nikpey et al, it was demonstrated in rats that there is an osmolite gradient from epidermis through dermis to subcutis. This study also demonstrated that lymph draining the skin is isosmotic to plasma. Earlier studies pertaining to this aspect were inconclusive (59). The presence of an osmolite gradient within the skin had already been previously demonstrated in a study using x-rays of the human skin (77). Moreover, in the 7T 23Na MRI study, it was shown that there is a greater accumulation of Na+ directly beneath the epidermis in comparison to the deeper layers of the dermis (78). Taking into account that greater Na+ accumulation occurred directly beneath the epidermis but was not associated with water accumulation, it has been hypothesized that the skin may contain a kidney-like countercurrent system with active transport of Na+ within the skin and with mobile macrophages acting as Na+ sensors. These would then have the potential to regulate lymphatic function in Na+ clearance via the TonEBP - VEGF-C - VEGFR3 axis (65,79,80). Further physiological studies are needed to confirm such presumptions.

CONCLUSIONS

The skin lymphatic system seems to be an integrated element of electrolyte and water homeostasis and plays a key role in the pathogenesis of hypertension. This new knowledge might be essential for the development of novel therapeutic options for hypertensive patients, especially those with salt-sensitive hypertension.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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