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NEW INSIGHTS INTO SALT-SENSITIVE HYPERTENSION

Abstract: *New insights into salt-sensitive hypertension*
Salt sensitivity, described as association between salt intake and blood pressure, varies among individuals. HSD contributes to salt-sensitive hypertension. Traditional view on blood pressure regulation was focused on the kidneys and ECV expansion secondary to body Na^+ load. However, the latest data suggest that salt-sensitive hypertension does not primarily come about by volume-related mechanisms and other than the renal body fluid control must play an important role. Since Na^+ accumulation in the body does not necessarily lead to expansion of the extracellular volume it is suggested that Na^+ might be stored in an osmotically inactive form either as osmotically inactive Na^+ storage in the skin and/or osmotically neutral Na^+/K^+ exchange in muscle. Hypertonicity in the skin interstitium compared with blood and therefore osmotic stress may be a crucial cause of interstitial Na^+ accumulation and hypertension development. Dietary salt loading increases osmotically inactive skin Na^+ storage and polyanionic character of the skin, leading to local hypertonicity. The response to this hypertonic internal environment in the skin interstitium involves MPS-driven and TonEBP–VEGF-C–mediated hyperplasia of lymph capillaries and increased eNOS expression. A decreased osmotically inactive storage capacity for Na^+ or reduced osmotically neutral Na^+/K^+ exchange may predispose to marked volume retention, and therefore to rise in blood pressure.

Key words: salt-sensitive hypertension, osmotically inactive Na^+ storage, mononuclear phagocyte system, vascular endothelial growth factor C

Hypertension contributes to increased morbidity and mortality due to increased risk of cardiovascular complications. Salt sensitivity indicates relationship between increasing salt intake and blood pressure and sensitivity to alterations in salt intake is variable among individuals.

Blood pressure depends on volume-dependent (extracellular fluid volume, ECV) and volume-independent (autonomic nervous system, vascular resistance) mechanisms. Traditional view on blood pressure regulation especially salt-sensitive hypertension was focused on the kidney which controls total body Na^+ and thereby extracellular volume. According to this view in a state of excessive salt intake the kidney prevents ECV expansion that could rise blood pressure

by rapid excess fluid and Na^+ eliminating. However, increased blood pressure and therefore the ECV expansion caused by reduced renal function, encourages a pressure natriuresis that corrects the body fluid volume change. Hence, ECV homeostasis is maintained at the expense of hypertension [1, 2]. Mineralocorticoid model of hypertension with Na^+ and water accumulation in the body also supports the renal-body fluid blood pressure regulation, since in positive Na^+ and water balances increased blood pressure stimulates pressure natriuresis. Thus a new steady state in Na^+ and water balance is achieved [3].

The currently favored a two-compartment model of fluid and electrolytes homeostasis relies on the notion that Na^+ is restricted mainly to the extracellular and K^+ to the intracellular fluid and as main osmotic cations hold water in the extracellular or intracellular space [4, 5]. The wide-spread concept underscores that extracellular body fluids which are represented as two distinct compartments, the interstitial and the intravascular spaces, are in equilibrium and interstitial Na^+ is mobilized into the bloodstream for renal Na^+ clearance [6, 7].

However, human Na^+ balance studies and experimental data suggest that high dietary Na^+ consumption with Na^+ accumulation in the body does not necessarily lead to expansion of the extracellular volume [8, 9] and negative Na^+ balance is not paralleled by volume losses [10]. This suggests that Na^+ might be stored in an osmotically inactive form. Farber and Soberman [11] were the first who speculated that Na^+ may be stored in an osmotically inactive form in "bone, cartilage, or connective tissue" or exchanged for some other intracellular cation.

40 years later Titze et al. imply that salt-sensitive hypertension does not primarily come about by volume-related mechanisms and other than the renal body fluid feedback control must play an important role in volume and blood pressure homeostasis [12].

DOCA salt is a widely accepted model for salt-sensitive hypertension [13]. Deoxycorticosterone-acetate (DOCA) reduces renal Na^+ excretion and increases total body sodium ($TBNa^+$) and total body volume (TBW). Secondary suppression of renin–angiotensin–aldosterone system [14] stimulates secretion of natriuretic peptides [15] and alters pressure natriuresis [3] establishing a new steady state between Na^+ intake and Na^+ excretion at a new blood pressure level. The kidneys escape the mineralocorticoid effect, and further salt retention stops, although at the expense of increased blood pressure [16].

Titze at al. show [17] that in DOCA rats given 1% saline only 20% of Na^+ accumulated is osmotic active and leads to water retention, whereas the rest is accumulated as water free by osmotically inactive Na^+ storage and/or osmotically neutral Na^+/K^+ exchange. $TBNa^+$ excess is not accompanied by corresponding TBW excess, thus water-free Na^+ accumulation prevents the rats from higher rTBW increase. Salt-sensitive hypertension is due to an increased susceptibility of the cardiovascular system to increase blood pressure at a given total body water content. This volume sensitivity of the cardiovascular system is caused by

increased sympathetic nerve activity and therefore increased peripheral vascular resistance [18] rather than increased cardiac output.

Additionally it is suggested that the redistribution of body electrolytes and water are important in the pathogenesis of salt-sensitive hypertension and is indicated that skin is a place of osmotically inactive Na^+ storage and muscle is a site where osmoltically neutral Na^+/ K^+ exchange takes place [19].

The skin contains a lot of interstitial glycosaminoglycans (GAGs), which are negatively charged polyanions that attract Na^+ and repel Cl^-. Recent data show that modification of the skin GAGs may play an important role in the regulation of osmotically inactive skin Na^+ storage as an extrarenal regulatory mechanism. Dietary salt loading increases osmotically inactive skin Na^+ storage and polyanionic character of the skin, leading to local hypertonicity [20]. Animals fed 8% NaCl diet or drink 1% NaCl have increased Na^+ content in the skin compared with low salt controls. However, water-free Na^+ retention is not paralleled by skin water accumulation or K^+ loss [21] confirming that the skin serves as an osmotically inactive Na^+ reservoir. Selective Na^+ accumulation without a parallel Cl^- increase fails to increase blood pressure [22, 23]. Rats receiving DOCA and 1% NaCl to drink compared to those with DOCA and drinking $NaHCO_3$ have similar average Na^+ retention, while higher mean arterial pressure. Skin Na^+ retention in excess over water in both DOCA-NaCl and DOCA-$NaHCO_3$ rats is paralleled by blood pressure increases, while plasma sodium concentrations are not changed [10]. Thus hypertonicity in the skin interstitium compared with blood and therefore osmotic stress may be a crucial cause of interstitial Na^+ accumulation and hypertension development.

Titze et al. also persuade that osmotically inactive Na^+ storage and/or local hypertonicity with DOCA-NaCl is not restricted to the skin but may also occur inside the muscle cell. They have found an osmotically neutral Na^+/K^+ exchange in the skeletal muscles, as evidenced by an increased Na^+ to water balance with concomitant decreases in the tissue K^+-to-water ratio [10, 12, 17]. Osmotically neutral Na^+/K^+ exchange challenges the view that Na^+ retention is restricted to the extracellular fluid volume.

Titze, thus, suggests three distinct regulatory levels that contribute to salt-sensitive hypertension: "(1) Na^+ balance sensitivity, which underscores the kidney's role in the maintenance of TBNa^+ homeostasis; (2) osmosensitivity, which determines whether or not a retained Na^+ load exerts osmotic activity and, hence, increases ECV; and (3) volume sensitivity, which indicates the cardiovascular susceptibility to generate blood pressure at a given total body water content. These regulatory levels contribute individually to DOCA salt hypertension when the rats are fed a high-salt diet" [12].

Basing on findings from experiments with Dahl rats [24] or the rats with ovariectomy (OVX) [12] researchers speculate that a decreased osmotically inactive storage capacity for Na^+ or reduced osmotically neutral Na^+/K^+ exchange may

predispose to marked volume retention, and therefore to the development of hypertension. High salt diet leads to Na^+ retention in salt-sensitive (SS) but not in salt-resistant (SR) Dahl rats. Both SS and SR strains have impaired storage of osmotically inactive Na^+ and SS rats are additionally characterized by a reduced ability to excrete Na^+ loads, with Na^+ accumulation and hypertension. Compared with DOCA salt rats, DOCA-OVX salt rats have higher blood pressure although Na^+ retention (balance sensitivity) and the blood pressure-volume association (volume sensitivity) does not differ between these groups. The major difference between DOCA salt rats and DOCA-OVX salt rats is at the level of osmosensitivity. OVX reduces the osmotically inactive Na^+ storage capacity, which increases volume retention despite similar Na^+ retention. An impairment in Na^+ accumulation in abundance over water goes along with further blood pressure rise in OVX-DOCA-salt-treated rats.

The latest data provide new insights into mononuclear phagocyte system (MPS) cell and lymphatic function in pathogenesis of salt-sensitive hypertension. Na^+-mediated osmotic differences between the interstitial fluid, the lymphatic environment and plasma stimulate macrophages in the skin interstitium to activate tonicity-responsive enhancer binding protein (TonEBP) [25]. TonEBP, an osmoprotective transcription factor, binds to the vascular endothelial growth factor C (VEGF-C) gene leading to hyperplasia of the lymph capillries in the interstitium and increased endothelial NO synthase (eNOS) expression in interstitial cells [26]. Inhibition of these processes by macrophage depletion or by blocking VEGF-C activity augments salt-sensitive hypertension, suggesting that MPS cells provide a buffering exrarenal mechanism for hypertension [27]. Different subtypes of MPS cells can evoke either proatherogenic (M1 subtypes) or antiatherogenic (M2 subtypes) effects [28]. MPS cells involved in regulation of volume and blood pressure homeostasis might represent an “M2 feature” and interstitial MPS infiltration may provide a protective effect against hypertension-induced target organ damage [27].

This article reviews the results and new theories concerning salt-sensitive hypertension from the studies performed by the group of Jens Titze from Erlangen-Nürnberg, Germany.

CONFLICT OF INTEREST STATEMENT

None declared.

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