Does Na\(^+\) really play a role in Ca\(^{2+}\) homeostasis in hypertension?

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CONTRACTION IS A CELLULAR event directly modulated by the cytoplasmic concentration of Ca\(^{2+}\), which binds to calmodulin, leading to the activation of myosin light chain kinase. The use of Ca\(^{2+}\) for intracellular signaling implies a tight local and global control of its cytoplasmic concentration and mechanisms for maintaining the cellular Ca\(^{2+}\) balance (17). Cytosolic Ca\(^{2+}\) signals are adjusted by entry and exit mechanisms, via plasma membrane Ca\(^{2+}\)-permeable channels and Ca\(^{2+}\) transporters, or by storage mechanisms, which include intracellular sources as the endo/sarcoplasmic reticulum (ER/SR) and Ca\(^{2+}\) binding proteins (14). Several membrane Ca\(^{2+}\)-permeable channels, which include receptor-operated, store-operated, voltage-gated, and stretch-activated channels (ROCs, SOCs, VGCs, and SACs, respectively) allow Ca\(^{2+}\) to enter the cell. In smooth muscle cells, Ca\(^{2+}\) is stored in the SR by the action of the sarco(endo)plasmic reticulum Ca\(^{2+}\)-ATPase. Extensive evidence indicates that a deficit in the regulation of Ca\(^{2+}\) influx through ROCs and SOCs, along with VGCs, plays a role in the augmented vascular reactivity, characteristic of clinical and experimental hypertension.

The family of classical or canonical transient receptor potential channels (TRPCs), which includes seven members (33), has been implicated to play a role in hypertension. Whereas TRPC3/6/7 channels, which are components of the ROCs, are activated by diacylglycerol, the regulation of the other members, TRPC1/2/4/5, which represent SOCs, as well as their activated by diacylglycerol, the regulation of the other members, TRPC3/6/7 channels, which are components of the ROCs, are still unclear (3, 7).

The authors (37) show that ASMCs from MHS display elevated resting cytosolic Ca\(^{2+}\), augmented ATP-induced Ca\(^{2+}\) signals, increased ROC-mediated Ca\(^{2+}\) entry (ROCE), along with increased expression of TRPC6 but not TRPC3, TRPC5, or TRPC1. Additionally, they demonstrated that alterations in Ca\(^{2+}\) regulation and TRPC6 expression occur simultaneously with the increased expression of the type 1 Na\(^{+}/\)Ca\(^{2+}\) exchanger (NCX1). The increased TRPC6 and NCX1 in ASMCs from MHS rats encoded increased cytosolic Ca\(^{2+}\) concentrations through ROCE-dependent mechanisms.

The idea that cations other than Ca\(^{2+}\) may contribute to Ca\(^{2+}\) homeostasis through ROC- and SOC-dependent mechanisms has been recently discussed by a number of investigators in the field. The link between Na\(^{+}\) and smooth muscle activation was first recognized in 1960 when Dodd and Daniel (10) reported that the removal of extracellular Na\(^{+}\) abolished agonist-induced constriction of the trachea and aorta. Later, Van Breemen’s group (26, 32) proposed that spontaneous Ca\(^{2+}\) release from the superficial SR is linked to Ca\(^{2+}\) extrusion via NCX at junctions of the plasma membrane and SR. Other evidence has supported that Na\(^{+}\) is a candidate to modulate Ca\(^{2+}\) influx (1, 27–28). Na\(^{+}\) may enter locally through ROCs and SOCs to promote Ca\(^{2+}\) extrusion via NCX (1, 4, 12, 27, 35).

Iwamot et al. (20) first identified the role of NCX1 in salt-sensitive hypertension using a specific NCX1 inhibitor. They elegantly showed that this drug was able to reduce arterial blood pressure in salt-dependent hypertensive rat models but not in other types of hypertension. They also showed that transgenic mice overexpressing NCX1 in smooth muscle cells were hypersensitive to salt (20).

The results from Zhang et al. (36) showed that NCX is functionally expressed in cultured human pulmonary ASMCs. They suggested that the activation of the reverse mode of NCX contributes to the Ca\(^{2+}\) influx via SOC (36). Latter, this group showed that pulmonary ASMCs from patients with idiopathic pulmonary arterial hypertension display an increased expression of NCX1, leading to enhanced Ca\(^{2+}\) entry. They suggested that NCX1 represents an additional mechanism responsible for the elevation of Ca\(^{2+}\) in pulmonary ASMCs from patients with idiopathic pulmonary arterial hypertension (35).

Most recently, Pulina et al. (28) showed that NCX is up-regulated in ouabain-induced hypertension. They also showed that these rats display increased cytosolic Ca\(^{2+}\), which is correlated with an augmented expression of the α2-subunit of the Na\(^{+}\) pump. Additionally, enhanced ROCE was observed in ASMCs from ouabain-hypertensive rats, along with an increased expression of TRPC6 (28). Finally, polymorphisms of NCX1 are predictors of essential hypertension in humans. Kokubo et al. (22) showed that genetic variations of NCX1 in
the Japanese population positively correlates with hypertension in men and women.

A functional coupling between the reverse-mode of NCX and TRPCs has been proposed to mediate Ca\(^{2+}\) influx via store-operated Ca\(^{2+}\) entry. Lemos et al. (23) localized Na\(^+\) elevations mediated by TRPC6 channels, which lead to Ca\(^{2+}\) influx through NCX channels. Syuoyng et al. (30) added a piece to this puzzle, showing that the functional coupling of TRPC6 and NCX also occurs via receptor-operated mechanisms. Purbuko et al. (27) found that local Na\(^+\) concentration transiently increases in ASMCs through TRPC6 channels. They showed that the local rise in Na\(^+\) concentration may drive Ca\(^{2+}\) into the myocytes via NCX (5, 27).

All these studies proposed a pathway that may explain the link between dietary salt and hypertension. For additional information, please review the following references (6, 16, 18–19, 21).

The report from Zulian and colleagues (37) on the mechanisms involved in Na\(^+\) and Ca\(^{2+}\) metabolism in arterial myocytes from MHS rats reinforces the idea that TRPC6 and NCX1 function as integrated units that help to regulate Ca\(^{2+}\) entry into vascular smooth muscle cells in salt-sensitive hypertension.

Given the increasing importance of the interrelationship among TRPC6, Na\(^+\) influx, NCX, and Ca\(^{2+}\) influx, it seems that this is not only a very promising research area but also the key to better understand the role of Na\(^+\) in hypertension, vascular reactivity, and blood pressure regulation.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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