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

Fernanda R. Giachini\textsuperscript{1,2} and Rita C. Tostes\textsuperscript{1,3}

\textsuperscript{1}Department of Physiology, Medical College of Georgia, Augusta, Georgia; \textsuperscript{2}Department of Pharmacology, University of Sao Paulo, Sao Paulo, Brazil; and \textsuperscript{3}Department of Pharmacology, Medical School of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Brazil

CONTRACTION IS A CELLULAR event directly modulated by the cytoplasmic concentration of Ca\textsuperscript{2+}, which binds to calmodulin, leading to the activation of myosin light chain kinase. The use of Ca\textsuperscript{2+} for intracellular signaling implies a tight local and global control of its cytoplasmic concentration and mechanisms for maintaining the cellular Ca\textsuperscript{2+} balance (17). Cytosolic Ca\textsuperscript{2+} signals are adjusted by entry and exit mechanisms, via plasma membrane Ca\textsuperscript{2+}-permeable channels and Ca\textsuperscript{2+} transporters, or by storage mechanisms, which include intracellular sources as the endo/sarcoplasmic reticulum (ER/SR) and Ca\textsuperscript{2+} binding proteins (14). Several membrane Ca\textsuperscript{2+}-permeable channels, which include receptor-operated, store-operated, voltage-gated, and stretch-activated channels (ROCs, SOCs, VGCs, and SACs, respectively) allow Ca\textsuperscript{2+} to enter the cell. In smooth muscle cells, Ca\textsuperscript{2+} is stored in the SR by the action of the sarco(endo)plasmic reticulum Ca\textsuperscript{2+}-ATPase. Extensive evidence indicates that a deficit in the regulation of Ca\textsuperscript{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 involvement in SR Ca\textsuperscript{2+} depletion is controversial (2, 8, 25, 34). There are three major theories to explain SOC-induced activation of TRPCs. In the first, inositol 1,4,5-trisphosphate binding to its receptor generates a conformational change in the structure of the TRPC channel (8). In the second, upon store depletion, the cytosolic influx factor signals the translocation of TRPCs to the membrane (9). The third implicates the recently discovered stromal interaction molecule (STIM), a protein that works as a Ca\textsuperscript{2+} sensor in the ER/SR. In conditions where the ER/SR is depleted, STIM1 is activated and induces Ca\textsuperscript{2+} influx through SOC/TRPCs (8, 15, 24, 29).

This issue of the \textit{American Journal of Physiology-Heart and Circulatory Physiology} brings an interesting report from Zulian and colleagues (37), who studied the regulation of Ca\textsuperscript{2+} homeostasis in arterial smooth muscle cells (ASMCs) from Milan hypertensive rats (MHS). This hypertensive animal model displays a polymorphism in a protein named adducin, which leads to higher Na\textsuperscript{+} pump activity and enhanced constitutive tubular Na\textsuperscript{+} reabsorption in the kidneys, resulting in a moderate elevation of blood pressure (11, 13, 31). Although the relationship between adducin alterations and renal dysfunc-

Address for reprint requests and other correspondence: Fernanda R. Giachini, Medical College of Georgia, 1120 15th St., CA 3101, Augusta, GA 30912-3000 (e-mail: fgiachini@mcg.edu).
the Japanese population positively correlates with hypertension in men and in 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. Syyong et al. (30) added a piece to this puzzle, showing that the functional coupling of TRPC6 and NCX also occurs via receptor-operated mechanisms. Porbuko 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\(^{2+}\) signals and regulate 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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