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COMMENT

# Vascular smooth muscle TRPV4 channel: a promising therapeutic target for salt-induced hypertension?

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Hypertension is associated with vascular resistance, which is characterized by multifactorial pathogenesis, including reduced endothelium-dependent vasorelaxation, enhanced vascular smooth muscle cell (VSMC) contraction, and vascular remodeling [1]. Accumulating evidence suggests that, during hypertension, dysregulation of ion channels and transporters in both endothelial cells (ECs) and SMCs shifts the membrane potential to a depolarized state, leading to a rise in the intracellular $Ca^{2+}$ concentration in VSMCs and thereby increasing vascular tone and blood pressure [1, 2].

Transient receptor potential (TRP) channels are non-selective cation channels located in virtually all tissues and are permeable to cations such as $Ca^{2+}$ and $Na^{+}$ [3, 4]. While several subfamilies of TRP channels, including TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), and TRPP (polycystin), have been identified in the vascular system and shown to regulate vascular tone mainly by modulating intracellular $Ca^{2+}$ concentrations and associated $Ca^{2+}$ responses [4], the EC TRPV4 channel has been a focus of attention in disease conditions such as hypertension [5] because of its wide expression in vascular ECs and its critical role in generating nitric oxide (NO) and endothelium-dependent hyperpolarization (EDH) [3–5]. Indeed, the causative link between the dysregulation of EC TRPV4 channels, endothelial dysfunction due to the loss of NO and/or EDH, and blood pressure elevation has been extensively explored in various models of hypertension, such as genetic hypertension, angiotensin II (Ang II)-induced hypertension, salt-induced hypertension, and hypertension with diet-induced obesity [5].

In addition to the pathophysiological involvement of EC TRPV4 channels in hypertension, emerging evidence sheds light on the role of VSMC TRPV4 channels in vasoconstriction and blood pressure elevation in some models of hypertension using cell-specific TRPV4 knockout mice [6, 7]. For example, in mesenteric arteries from Ang II-infused hypertensive mice, VSMC TRPV4 channels contribute to blood pressure elevation through two distinct mechanisms of action: an elevated α1 adrenergic receptor/protein kinase Cα/TRPV4-mediated vasoconstriction and an impaired TRPV4/large conductance $Ca^{2+}$-activated $K^{+}$ channels mediated vasorelaxation [6]. Moreover, in mesenteric arteries from high-fat diet-induced obese mice, VSMC TRPV4 channels contribute to blood pressure elevation by promoting actin cytoskeleton polymerization through an activation of small GTPase Rho [7].

In this issue of *Hypertension Research*, Wen et al. add a novel perspective on the role of the VSMC TRPV4 channel on vasoconstriction and blood pressure elevation in high salt-induced hypertension [8]. While a previous study has shown that EC TRPV4 channels mediate endothelium-dependent VSMC contraction through the production and release of cyclooxygenase-derived endothelium-dependent contracting factors in the aorta of salt-induced hypertensive mice [9] (Fig. 1), the present study by Wen and colleagues using genetically manipulated mice lacking EC TRPV4 channels unambiguously demonstrates a novel role of VSMC TRPV4 channels in the aortic VSMC contraction during salt-induced hypertension [8]. The authors explore further to reveal the underlying molecular mechanisms, and demonstrate that a high-salt diet increases the expression and function of aortic VSMC TRPV4 channels, which subsequently transcriptionally upregulates the expression of interferon regulatory factor 7 (IRF7), leading to an induction of inositol 1,4,5-trisphosphate receptor type 2 ($IP_3R2$)

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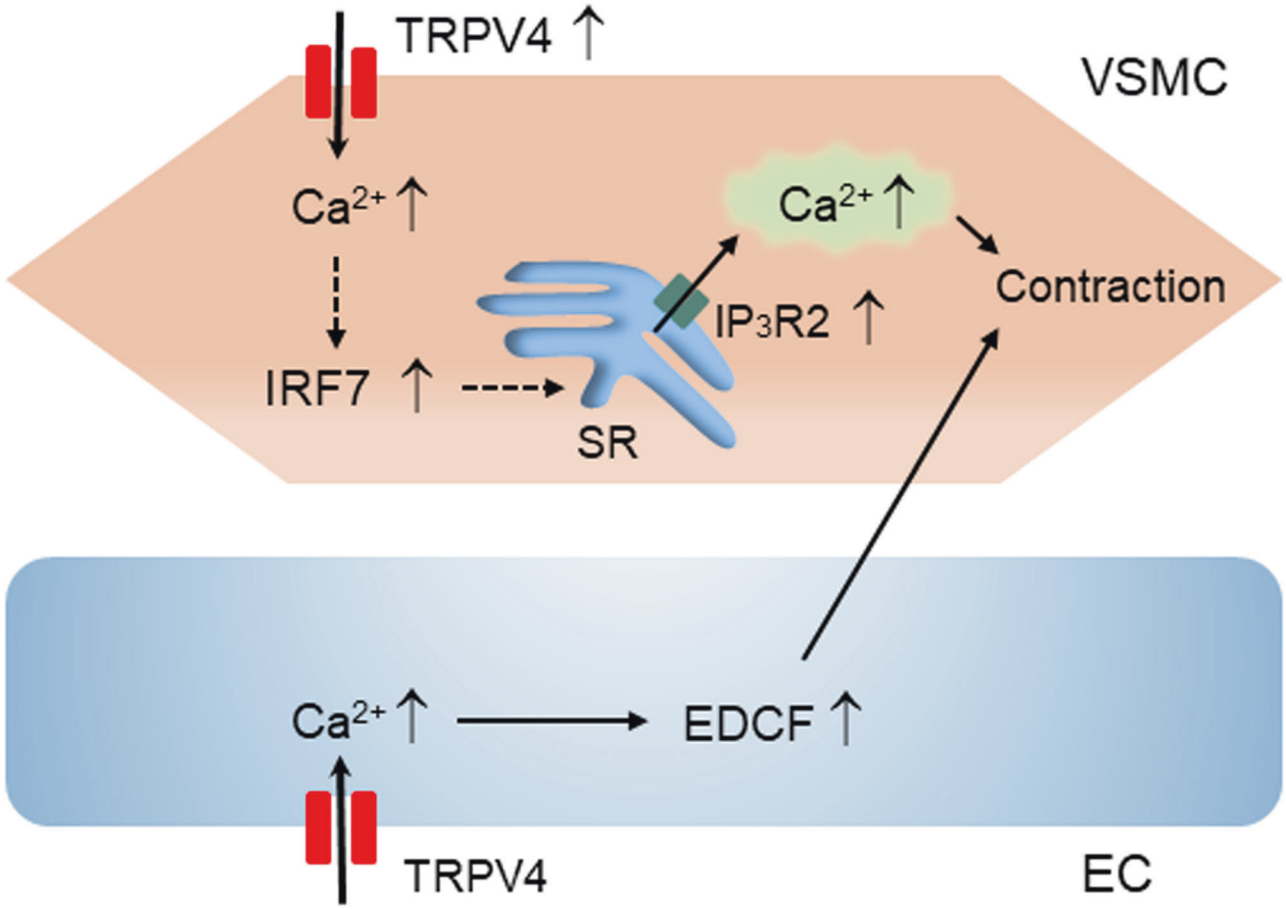
**Graphical Opinion**




and associated contractile $Ca^{2+}$ release from the aortic VSMC sarcoplasmic reticulum (Fig. 1). The results of the present study indicate that VSMC TRPV4 channels, IRF7, and $IP_3R2$ are novel modulators of VSMC contraction and may represent promising therapeutic targets for hypertension and hypertension-associated vascular dysfunction induced by high salt intake.

Although the pathophysiological contribution of the TRPV4/IRF7/$IP_3R2$ signaling to VSMC contraction has been systematically investigated in the present study, several important questions remain to be answered. First, the underlying mechanisms by which TRPV4 channels upregulate and stimulate both IRF7 and $IP_3R2$ in aortic VSMCs are unclear and require further elucidation. In particular, because some studies have indicated that IRF7 plays pathophysiological roles in cardiovascular diseases [10], there is a need for in-depth investigations to identify the expression profiles and function of IRF7 in aortic VSMCs from high-salt intake hypertensive mice, which could improve our understanding of salt-induced vascular dysfunction. Secondly, the endogenous activator of aortic VSMC TRPV4 channels in salt-induced hypertension is not explored in the present study. While VSMC TRPV4 channels in mouse mesenteric resistance arteries are activated by α1-adrenergic receptor signaling in Ang II-induced hypertension [6] and by mechanical force in high-fat diet-induced hypertension [7], it is unknown whether such mechanisms contribute to the activation of VSMC TRPV4 channels during salt-induced hypertension in an elastic artery such as the aorta. Finally, caution should be exercised in that the treatment of mice with a concomitant intake of a high-salt diet and N-nitro-L-arginine (a NO synthase inhibitor), as in the present study, may render aortic VSMC vulnerable to vasoconstrictor stimuli; under this specific treatment condition, endothelium-dependent NO production should be severely diminished, and therefore, would be expected to result in facilitation of the VSMC TRPV4 channel-mediated aortic contraction.

Intriguingly, Gao et al. [11] have reported that the treatment of Dahl salt-resistant rats with intake of a high-salt diet alone increases TRPV4 expression in the mesenteric arteries, and the increased TRPV4 channels act to reduce blood pressure probably by activating EDH, suggesting that the upregulation of endothelial TRPV4 channels and the

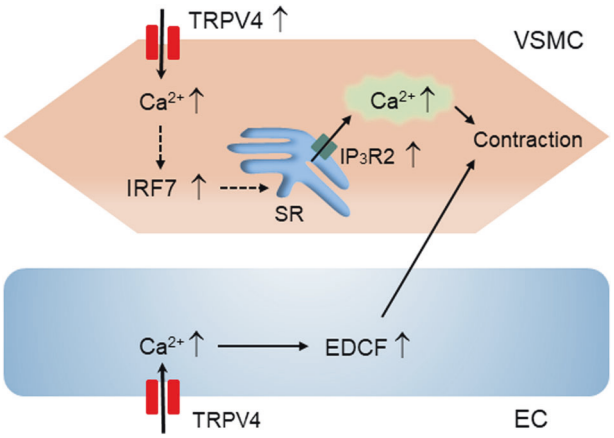



**Fig. 1** A schematic diagram of transient receptor potential vanilloid type 4 (TRPV4)-mediated vasoconstriction in the aorta of mice fed a high-salt diet. A high-salt diet increases the expression and function of aortic vascular smooth muscle cell (VSMC) TRPV4 channels, which in turn upregulates the expression of both interferon regulatory factor 7 (IRF7) and inositol 1,4,5-trisphosphate receptor type 2 ($IP_3R2$), leading to an increased release of contractile $Ca^{2+}$ from the sarcoplasmic reticulum (SR) and resultant vasoconstriction. In parallel, a high-salt diet facilitates the endothelial cell (EC) TRPV4 channel-dependent production and release of cyclooxygenase-derived endothelium-dependent contracting factor (EDCF), which further augments the aortic VSMC contraction in salt-induced hypertension. (↑) Increased or Activation

subsequent activation of EDH function as a compensatory mechanism limiting high-salt induced vasoconstriction and blood pressure elevation [11]. Thus, it would be of great interest to conduct further studies evaluating the potential EC–VSMC TRPV4 channels interaction during high-salt intake, preferably in intact resistance arteries, which would further clarify the pathophysiological role of the VSMC TRPV4 channel in the regulation of vascular tone and blood pressure in salt-induced hypertension.

Notwithstanding these unresolved issues, the present novel findings by Wen and colleagues are of clinical importance in light of the fact that the dysregulation of VSMC TRPV4 channels contributes to increased contraction of resistance arteries and blood pressure elevation in patients with hypertension [6], and may open a new avenue in research targeting the VSMC TRPV4 channel for the prevention and treatment of salt-induced hypertension and associated vascular diseases.

## Compliance with ethical standards

**Conflict of interest** The author declares no competing interests.

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