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PERSPECTIVE

The heat is on! TRPV1 channels and resistance artery myogenic tone

William F. Jackson
Department of Pharmacology and Toxicology, College of Osteopathic Medicine, Michigan State University, East Lansing, MI, USA

Email: jacks783@msu.edu

Edited by: Don Bers & Calum Wilson

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Myogenic tone is a hallmark feature of resistance arteries and arterioles. This pressure-induced contractile activity of vascular smooth muscle cells sets the resting diameter of resistance arteries and arterioles such that they can dilate or constrict to regulate their hydraulic resistance controlling blood flow to and within the body's tissues and organs, thus maintaining homeostasis. Despite the fundamental importance of myogenic tone to the physiology of the cardiovascular system in health and disease, our understanding of the mechanisms responsible for myogenic tone remains incomplete. Increased luminal pressure (P) in a cylindrical blood vessel with internal radius (r) and wall thickness (Δ) will increase tangential wall stress (T) as described by the law of Laplace ($T = P \times r/\Delta$). Increased wall stress will stretch (cause strain in) the vascular smooth muscle cells and extracellular matrix in the vessel wall and cause passive dilatation until either the passive wall stress (as a result of collagen, elastin, cytoskeletal elements, etc.) matches the pressure-induced stress, or the vascular smooth muscle cells can generate sufficient active stress to match or overcome the pressure-induced wall stress. What senses the wall stress/strain and the signal-transduction cascade beyond the sensor remains to be determined (Jackson, 2021). Phan *et al.* (2022) add transient receptor potential vanilloid family member 1 (TRPV1) channels to the growing list of ion channels implicated in myogenic tone in resistance arteries and arterioles (Jackson, 2021). Following up on their study demonstrating functional expression of TRPV1 channels in skeletal muscle and coronary resistance artery and arteriole smooth muscle cells (Phan *et al.*, 2020), they show that, in these vascular beds, TRPV1 channels contribute substantially to the rate and magnitude of myogenic tone development and that deactivation of these channels is essential for reactive vasodilatation that follows vasoconstriction.

These findings have implications beyond the pressure-induced myogenic response and myogenic tone. For example, skeletal muscle arterioles are exquisitely sensitive to changes in O_2 partial pressure in their environment with increases in P_{O2} in the physiological range of 15–100 mmHg causing vasoconstriction that is mediated by 20-hydroxyeicosatetraenoic acid (20-HETE), vascular smooth muscle depolarization and activation of nifedipine-sensitive voltage-gated Ca^{2+} channels (VGCCs) (Jackson, 2016). TRPV1 channels are activated by 20-HETE (Wen *et al.*, 2012), suggesting that these channels also probably participate in skeletal muscle arteriolar O_2 reactivity. Are TRPV1 channels also a target for 20-HETE in the coronary circulation? What other signalling pathways converge on TRPV1 channels to modulate their function in the heart and skeletal muscle vasculature?

The signalling pathway (pressure → $G_{q/11}$-coupled receptor → phospholipase C → diacylglycerol → protein kinase C → increased heat sensitivity of TRPV1) for pressure-induced activation of TRPV1 channels proposed by Phan *et al.* (2020) also has implications for vasoconstriction mediated by other $G_{q/11}$-protein coupled receptors. Are vascular smooth muscle TRPV1 channels involved in vasoconstriction produced by agonist-induced activation of α_1-adrenergic receptors, endothelin A receptors and vasopressin 1 receptors, etc., that link to $G_{q/11}$ proteins in coronary and skeletal muscle resistance arteries and arterioles?

It also will be interesting to determine how TRPV1 channels interact with other ion channels that have been implicated in myogenic tone (Jackson, 2021). For example, inositol 1,4,5 trisphosphate receptors (IP_3Rs) produce pressure-induced Ca^{2+} signals (Ca^{2+} waves) that contribute to myogenic tone in skeletal muscle resistance arteries and arterioles (Jackson, 2021). Does Ca^{2+} influx through TRPV1 channels directly contribute to the activation of IP_3Rs and Ca^{2+} waves? Does Ca^{2+} influx through TRPV1 channels directly activate other Ca^{2+}-activated ion channels such as Ca^{2+}-activated Cl^- channels (a positive feedback signal, amplifying membrane depolarization) or large-conductance Ca^{2+}-activated K^+ channels (a negative feedback signal that dampens membrane depolarization) (Jackson, 2021)?

Defining the precise role played by protein kinase C (PKC) in vascular myogenic tone in the heart and skeletal muscle will require further study. In addition to TRPV1 channels and transient receptor potential melanostatin family member 4 (i.e. TRPM4) channels noted by Phan *et al.* (2022), PKC isoforms are well established to increase the activity of CaV1.2 VGCCs and inhibit several K^+ channels, all of which contribute to myogenic tone in resistance arteries (Jackson, 2021). PKC can also inhibit myosin light-chain phosphatase producing Ca^{2+} sensitization of the contractile machinery and promote remodelling of the actin cytoskeleton, which may contribute to myogenic tone (Jackson, 2021). How do these other PKC targets integrate with the function of TRPV1 channels with respect to determining myogenic tone?

Answering these and additional questions that arise from the findings of Phan *et al.* (2022) will require additional research using multiple methods, including patch clamp recording of membrane currents, biochemical assessment of protein phosphorylation and protein–protein interactions, sharp electrode or optical recording of membrane potential, high-speed Ca^{2+} imaging, pressure myography and intravital imaging of resistance arteries and arterioles that develop myogenic tone in vascular beds around the body. These studies will help to place the findings reported by Phan *et al.* (2022) regarding TRPV1 channels in context with the growing body of evidence indicating that an expanding list of ion channels and signalling pathways contribute to the myogenic response, myogenic tone and their modulation in the resistance vasculature.

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Additional information

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Author contributions

WFJ conceived, wrote and edited this manuscript and is solely responsible for its content. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

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Supporting information

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