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EDITORIAL

Mechanosensitive Angiotensin II Receptor Signaling in Pressure-Induced Vasoconstriction

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Angiotensin II (Ang II) type 1 receptors (AT1R) in the kidneys are the primary mediators of Ang II-induced hypertension.[1] The effects of Ang II have been attributed mainly to the $G_{q/11}$-coupled AT1a receptor (AT1aR) subtype, although AT1b receptors (AT1bR) are also expressed in blood vessel walls.[2] Recent studies support the concept that AT1aR is a mechanosensitive receptor in smooth muscle cells (SMCs) and plays a vital role in intraluminal pressure-induced (myogenic) vasoconstriction.[3] However, the relative contributions of $G_{q/11}$ protein signaling and noncanonical β-arrestin signaling in AT1aR regulation of myogenic vasoconstriction were unknown. A study published by Cui and colleagues in this issue of the *Journal of the American Heart Association* (*JAHA*) proposes that G proteins q/11 subunits ($G_{q/11}$)-dependent signaling pathways, but not β-arrestin-dependent signaling, play a vital role in AT1aR-induced development of myogenic vasoconstriction (Figure).[4] Although AT1bR has also been implicated in myogenic vasoconstriction, the authors present data that AT1bR deletion does not affect vasoconstriction in mouse renal arterioles.[4] Notably, the use of tamoxifen-inducible, SMC-specific, AT1aR knockout (SMMHC-Cre+Agtr1a$^{-/-}$) mice in this study has resulted in definitive evidence that AT1aR is essential for myogenic constriction of cerebral, mesenteric, and renal arteries. While pressure myography is a well-established standard for studying the effect of intraluminal pressure on arterial contraction, the studies in isolated perfused kidneys are physiologically more relevant. Collectively, the findings in the article by Cui et al support the idea that SMC AT1aRs play a critical role in pressure-induced vasoconstriction but do not influence cardiac function.[4] Understanding the signaling linkages of AT1aRs in myogenic vasoconstriction will be a crucial next step in the process of developing therapeutic strategies against hypertension.

See Article by Cui et al.

More than a century ago, Bayliss reported intraluminal pressure-induced vasoconstriction as an autoregulatory mechanism in small arteries.[5] Several signaling mechanisms have been proposed as mediators of myogenic vasoconstriction. Two events appear to be absolutely crucial for the development of myogenic vasoconstriction: SMC membrane depolarization and subsequent activation of voltage-gated Ca^{2+} channels. Over the past 2 decades, research efforts have focused on deciphering the mechanisms for intraluminal pressure-induced depolarization of SMC membranes. The activation of Piezo1, transient receptor potential melastatin 4 (TRPM4), and TRP canonical 6 (TRPC6) channels on SMC membranes has emerged as key events in pressure-induced SMC membrane depolarization. More recent studies show that mechanosensitive TRPM4 and Piezo1 channels could be critical players in pressure-induced membrane depolarization of SMCs.[6] Whether AT1aR is also involved in pressure-induced membrane depolarization or acts downstream of depolarization is

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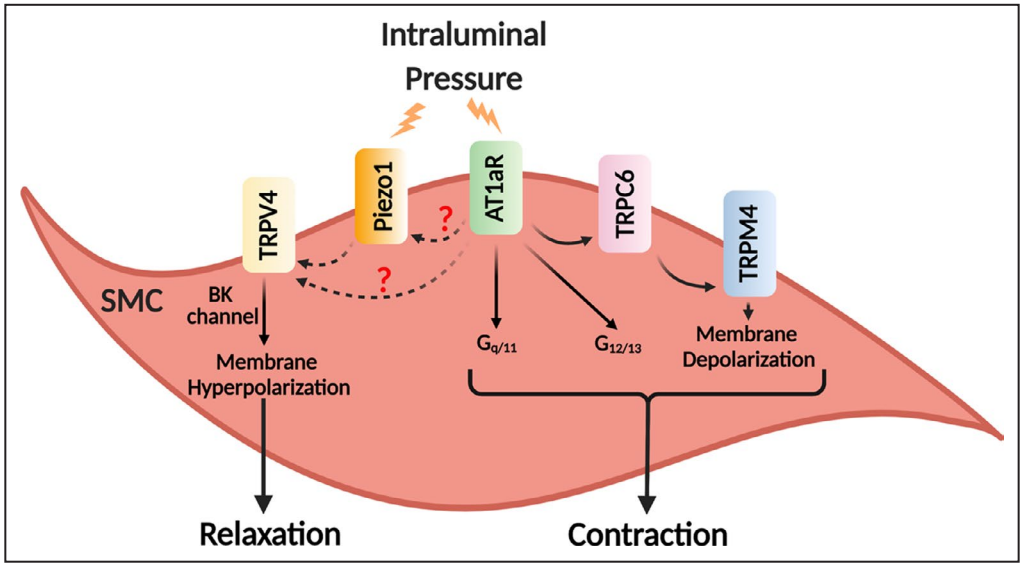

Figure. Schematic diagram showing AT1aR-dependent signaling activated by intraluminal pressure. Intraluminal pressure induces vascular smooth muscle cells (SMC) contraction via AT1aR activation and $G_{q/11}$ signaling. Activation of AT1aRs elicits TRPC6 channel–TRPM4 channel signaling and membrane depolarization. The figure also shows potential signaling linkages of AT1aRs with TRPV4 and Piezo1 channels on the SMC membrane. AT1aR indicates angiotensin II 1a receptor subtype; BK channel, Ca^{2+}-activated large-conductance K^+ channel; $G_{12/13}$, G proteins 12/13 subunits; $G_{q/11}$, G proteins q/11 subunits; TRPC6, transient receptor potential canonical 6; TRPM4, transient receptor potential melastatin 4; and TRPV4, transient receptor potential vanilloid 4.

not clear. In this regard, Gonzales and colleagues recently showed that pressure-induced AT1R activation could lead to the opening of TRPC6 channels and influx of Ca^{2+} in SMCs, which in turn activates TRPM4 channels and results in SMC membrane depolarization.[7] Collectively, the literature supports an essential role of AT1aR, Piezo1 channels, TRPC6 channels, and TRPM4 channels in the development of myogenic vasoconstriction. Signaling interactions among these proteins will be an exciting area for future investigations.

Several ion channels in SMCs could potentially interact with AT1aRs to modulate myogenic vasoconstriction. Harraz et al demonstrated that Ca^{2+} influx through T-type Ca^{2+} channels is essential for the development of myogenic vasoconstriction in mesenteric arteries.[8] Another TRP channel, TRP vanilloid 4 (TRPV4), is unlikely to be a direct mechanosensor,[9] but is activated by increased intraluminal pressure in SMCs.[10] Intriguingly, Swain and colleagues reported that Piezo1 channels can stimulate TRPV4 channel activity in pancreatic acinar cells.[11] Studies by Crnich and colleagues also support a role for the transient receptor potential mucolipin channels in the development of myogenic vasoconstriction.[12] Thus, multiple ion channels and receptors are involved in the development of intraluminal pressure-induced vasoconstriction. Considering the findings of Cui and colleagues that the development of myogenic vasoconstriction is impaired in SMC-specific AT1aR knockout mice,[4] it is conceivable that AT1aR interacts with 1 or more of these ion channels and other signaling elements involved in myogenic vasoconstriction.

Cui and colleagues propose that the effects of AT1aR are transduced by $G_{q/11}$ proteins.[4] However, the specific signaling events downstream of $G_{q/11}$ activation are unclear. For example, AT1aR stimulation will result in inositol 1,4,5-trisphosphate (IP3) release and IP3 receptor (IP3R) activation in SMCs.[13] IP3R activation will increase Ca^{2+} release from the sarcoplasmic reticulum, ultimately contracting the SMCs.[13] Increased intracellular Ca^{2+} can also activate Ca^{2+}-regulated channels, including TRPM4 and TRPV4 channels, on the SMC membrane. Additionally, $G_{q/11}$ signaling will activate phospholipase C, thereby breaking down phosphatidylinositol 4,5-bisphosphate and increasing the levels of diacylglycerol.[14] Diacylglycerol is the endogenous activator of TRPC6 channels and can promote myogenic vasoconstriction through TRPC6 channel activation.[15] Moreover, phosphatidylinositol 4,5-bisphosphate has been identified as an endogenous inhibitor of TRPV4 channel activity.[16] Diacylglycerol also activates protein kinase C, which can phosphorylate and regulate the activity of several ion channels involved in the development of myogenic vasoconstriction. Protein kinase C has been shown to phosphorylate and activate L-type Ca^{2+} channels and TRPV4 channels.[17] Thus, AT1aR signaling can potentially regulate the intricate network of ion channels involved in the development of myogenic vasoconstriction.

Co-localization of AT1Rs with ion channels and other signaling elements will be a major consideration as we

further investigate the AT1R-dependent signaling pathways in SMCs. SMC membrane contains functionally important signaling nano/microdomains facilitated by spatial co-localization of interacting proteins. The proximity of the signaling elements determines their coupling and, ultimately, the effect on SMC contraction. For example, the coupling of ryanodine receptors with Ca^{2+}-activated, large-conductance K^+ (BK) channels negatively regulates myogenic constriction,[18] whereas the coupling of voltage-gated Ca^{2+} channels with IP3Rs promotes SMC contraction.[19] Similarly, spatial proximity of TRPV4 channels or T-type Ca^{2+} channels with ryanodine receptors can limit SMC contraction.[8,18] Therefore, studies investigating the ion channels and other proteins in spatial proximity with AT1aR may provide new insights on the signaling linkages of AT1aR in SMCs. Chennupati and colleagues recently reported the involvement of G proteins 12/13 subunits (G_{12}/G_{13})-dependent pathways in modulating vasoconstriction and maintaining vascular resistance via Rho-dependent pathway under physiological and pathological conditions (Figure).[20] Therefore, a role for the interaction between $G_{q/11}$- and $G_{12/13}$-dependent signaling in myogenic vasoconstriction cannot be ruled out.

Significant progress has been made in understanding the specific role of AT1aR in the development of myogenic vasoconstriction, although the role of AT1aR-dependent signaling in resting blood pressure regulation remains unclear. Individual elements of AT1aR-dependent signaling could also be involved in excessive vasoconstriction commonly observed in cardiovascular disorders, a possibility that remains unexplored. Considering the importance of AT1aR signaling in myogenic vasoconstriction, targeting individual elements of this signaling pathway may result in therapeutic benefit in hypertension. Future investigations in this direction are likely to further our understanding of AT1aR-dependent mechanisms in myogenic vasoconstriction, their physiological significance, and involvement in disease pathogenesis.

ARTICLE INFORMATION

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