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. The effects of Ang II have been attributed mainly to the $\alpha_{11}$-coupled AT1a receptor (AT1aR) subtype, although AT1b receptors (AT1bR) are also expressed in blood vessel walls. 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. However, the relative contributions of $G_{q/11}$ protein signaling and noncanonical $\beta$-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 $G_{q/11}$-dependent signaling pathways, but not $\beta$-arrestin-dependent signaling, play a vital role in AT1aR-induced development of myogenic vasoconstriction (Figure). Although AT1bR has also been implicated in myogenic vasoconstriction, the authors present data that AT1bR deletion does not affect vasoconstriction in mouse renal arterioles. 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. Understanding the signaling linkages of AT1aRs in myogenic vasoconstriction will be a crucial next step in the process of developing therapeutic strategies against hypertension.

More than a century ago, Bayliss reported intraluminal pressure-induced vasoconstriction as an autoregulatory mechanism in small arteries. 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 Ca²⁺ 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. Whether AT1aR is also involved in pressure-induced membrane depolarization or acts downstream of depolarization is...
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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, TRPV4 (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
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REFERENCES
1. Crowley SD, Gurley SB, Herrera MJ, Ruiz P, Griffiths R, Kumar AP, Kim HS, Smithies O, Le TH, Coffman TM. Angiotensin II causes hypertension and cardiac hypertrophy through its receptors in the kidney. Proc Natl Acad Sci USA. 2006;103:17985–17990. doi: 10.1073/pnas.0605545103
2. Zhou Y, Chen Y, Dirksen WP, Morris M, Periasamy M. AT1b receptor predominantly mediates contractions in major mouse blood vessels. Circ Res. 2003;93:1089–1094. doi: 10.1161/01.RES.000010912.01071. Fr
3. Schleifenbaum J, Kassmann M, Szijarto IA, Hercule HC, Tano JY, Weinert S, Heidenreich M, Pathan AR, Anistan YM, Alenina N, et al. Stretch-activation of angiotensin II type 1a receptors contributes to the myogenic response of mouse mesenteric and renal arteries. Circ Res. 2014;115:263–272. doi: 10.1161/CIRCRESAHA.113.302882
4. Cui Y, Kassmann M, Nickel S, Zhang C, Alenina N, Anistan YM, Schleifenbaum J, Bader M, Welsh DG, Huang Y, et al. Myogenic vasoconstriction requires canonical Gα11 signaling of the angiotensin II type 1 receptor. J Am Heart Assoc. 2022;10:e022070. doi: 10.1161/JAHA.121.022070
5. Bayliss WM. On the local reactions of the arterial wall to changes of internal pressure. J Physiol. 1902;28:220–231. doi: 10.1113/jphysiol.1902.sp000911
6. Coste B, Mathur J, Schmidt M, Earley TJ, Ranade S, Petrus MJ, Dubin AE, Patapoutian A. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. Science. 2010;330:55–60. doi: 10.1126/science.1193270
7. Gonzales AL, Yang Y, Sullivan MN, Sanders L, Dabertrand F, Hill-Eubanks DC, Nelson MT, Earley S. A PLCγ1-dependent, force-sensitive signaling network in the myogenic constriction of cerebral arteries. Sci Signal. 2014;7a49. doi: 10.1126/scisignal.2004732
8. Harraz OF, Brett SE, Zechariah A, Romero M, Puglisi JL, Wilson SM, Welsh DG. Genetic ablation of CaV3.2 channels enhances the arterial myogenic response by modulating the RyR-BKCa axis. Arterioscler Thromb Vasc Biol. 2015;35:1843–1851. doi: 10.1161/ATVBAHA.115.305736
9. Chen YL, Sonkusare SK. Endothelial TRPV4 channels and vasodilator reactivity. Curr Top Membr. 2020;85:89–117.
10. Chen YL, Daneva Z, Kuppusamy M, Ottolino M, Klimentova E, Sonkusare SK. Regulation of blood pressure by smooth muscle TRPV4 channels under normal and hypertensive conditions. Circulation. 2021;144:A12772. doi: 10.1161/circ.114.supp1.I12772
11. Swain SM, Romac JM, Shahid RA, Pandol SJ, Liedtke W, Vigna SR, Liddle RA. TRPV4 channel opening mediates pressure-induced pancreaticitis initiated by Piezo1 activation. J Clin Invest. 2020;130:2527–2541. doi: 10.1172/JCI134111
12. Crnich R, Amberg GC, Leo MD, Gonzales AL, Tamkun MM, Jaggar JH, Earley S. Vasoconstriction resulting from dynamic membrane trafficking of TRPM4 in vascular smooth muscle cells. Am J Physiol Cell Physiol. 2010;299:C682–C694. doi: 10.1152/ajpcell.00110.2010
13. Alexander RW, Brock TA, Gibbona MA Jr, Rittenhouse SE. Angiotensin increases inositol trisphosphate and calcium in vascular smooth muscle. Hypertension. 1985;7:447–451. doi: 10.1161/01.HYP.7.3.447
14. Goldsmith ZG, Dhanasekaran DN. G protein regulation of MAPK networks. Oncogene. 2007;26:3122–3142. doi: 10.1038/sj.onc.1210407
15. Aries V, Hichami A, Boulay G, Khan NA. Activation of TRPC6 calcium channels by diallylglycerol (DAG)-containing arachidonic acid: a comparative study with DAG-containing docosahexaenoic acid. Biochimie. 2007;99:926–937. doi: 10.1016/j.bioch.2006.10.016
16. Harraz OF, Longden TA, Hill-Eubanks DC, Nelson MT. PIP2 depletion promotes TRPV4 channel activity in mouse brain capillary endothelial cells. eLife. 2018;7:e38689. doi: 10.7554/eLife.38689
17. Mercado J, Bayle R, Navedo MF, Yuan C, Scott JD, Nelson MT, Brayden JE, Santana LF. Local control of TRPV4 channels by AKAP150-targeted PKG in arterial smooth muscle. J Gen Physiol. 2014;143:559–575. doi: 10.1085/jgp.201311050
18. Earley S, Heppner TJ, Nelson MT, Brayden JE. TRPV4 forms a novel Ca2+ signaling complex with ryanodine receptors and BKCa channels. Circ Res. 2005;97:1270–1279. doi: 10.1161/01.RES.0000194321.80300.0d
19. Ghosh D, Syed AL, Prada MP, Nystoriak MA, Santana LF, Nieves-Cintron M, Navedo MF. Calcium channels in vascular smooth muscle. Adv Pharmacol. 2017;78:49–87. doi: 10.1016/bs.apha.2016.08.002
20. Chennupati R, Wirth A, Favre J, Li R, Bonnavage R, Jin YJ, Wietelmann A, Schweda F, Wettachureck N, Herrin D, et al. Myogenic vasoconstriction requires G12/G13 and LARG to maintain local and systemic vascular resistance. eLife. 2019;8:e49374. doi: 10.7554/eLife.49374

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