The myogenic response is an intrinsic vascular response characterized by vasoconstriction in response to increases and vasodilation to decreases in perfusion pressure. Recent studies suggest this response may play a significant role in the protection of the renal microcirculation from pressure dependent injury, especially with concomitant renal disease. Although the myogenic response was first described more than 100 years ago, the molecular mechanisms underlying the transduction of pressure into a cellular event (i.e., vasoconstriction) in vascular smooth muscle cells (VSMCs) has remained elusive. Several potential molecules with a connection to mechanosensitive responses have been identified including integrins, transient receptor potential (TRP) channels, and members of the Epithelial Sodium Channel (ENaC) family. Members of the ENaC family have received recent attention because of evidence for and against a role for ENaC proteins in myogenic constriction in the renal circulation. The current study by Guan et al helps to address the controversial role of ENaC in afferent arteriolar myogenic constriction.

ENaC and closely related Acid Sensing Ion Channel (ASIC) proteins are considered potential mechanotransducers in VSMCs because of their strong evolutionary connection to a group of proteins termed degenerins. The degenerins are a group of nematode Caenorhabditis elegans proteins that comprise the ion channel pore in a large multimeric mechanosensory complex. Genetic evidence suggests the pore forming degenerins are tethered to the cytoskeleton and extracellular matrix and aid in force transduction. The extracellular matrix, linking proteins, and cytoskeletal proteins are required for proper mechanosensor channel activation. An analogous mechanotransducer model in mammals has also been proposed (Figure 1A). Although many scientists consider ENaC proteins to be restricted to epithelial cells, ENaC expression has been repeatedly identified in many other cell types, including VSMCs.

Several studies support a role for ENaC proteins as mediators of myogenic responsiveness in renal interlobar and middle cerebral arteries. ENaC proteins are expressed in VSMCs from several circulatory systems. Furthermore, ENaC inhibition (amiloride or its lipophilic analog benzamil) or gene silencing (using overexpression of dominant-negative ENaC isoforms or siRNA) blocks myogenic constriction in response to an increase in pressure. At least pharmacological blockade also blocks resting myogenic tone. Thus, the initial studies on the role of ENaC as a mediator of myogenic response in renal vessels suggest ENaC proteins may act as mediators of myogenic response. A schematic illustrating the potential role of ENaC in myogenic constriction based on our current understanding of myogenic signaling cascade is provided in Figure 1B.

A limitation of these studies is that they were conducted in renal interlobar arteries (50 to 100 μm resting diameter). While interlobar arteries have a myogenic response, the major site of renal vascular resistance is the afferent arteriole. The myogenic response can be studied in afferent arterioles using isolated arterioles and whole kidney approaches, however each approach presents individual challenges. Studies in isolated afferent arterioles are technically demanding, and isolating the afferent arteriole from the surrounding extracellular matrix may disrupt components of the gating mechanism (noted in the preceding paragraph), so negative results from studies with this approach may not be informative. The importance of ENaC in myogenic constriction has not been addressed using this model. Studies using whole kidney perfusion approaches are also possible, but care must be taken to prevent contribution of the tubuloglomerular feedback mechanism (TGF, pressure-dependent increases in Na+ delivery to macula densa cells elicits afferent arteriolar vasoconstriction). The hydronephrotic kidney and the juxtamedullary nephron preparation are 2 models that allow for whole kidney evaluation of afferent myogenic responses.

In the hydronephrotic kidney, chronic (6 to 8 weeks) ureteral ligation induces tubular atrophy, which abolishes TGF and allows visualization of the afferent arteriole. Using this preparation, a recent study by Wang et al demonstrated no contribution of ENaC to myogenic function in rat afferent arterioles and further demonstrated little to no message for ENaC transcripts in isolated afferent arterioles. Findings of this study do not support a role for ENaC proteins in afferent arteriole myogenic constriction. However, the recent findings of Guan et al stand in contrast to those of Wang et al. Guan et al localized expression of ENaC proteins in pregglomerular VSMCs using immunolocalization and demonstrated pharmacological ENaC blockade inhibited myogenic constriction in rat afferent arterioles using an isolated blood-perfused juxtamedullary nephron preparation in which effects of TGF were eliminated by a papillectomy. So, what factor(s) might explain the contrasting results? Although the answer to this question is not clear, one possibility is the animal model (hydronephrotic kidney versus juxtamedullary nephron prep-
Further studies are needed to clarify the conditions and importance of ENaC proteins in afferent arteriolar myogenic constriction.

The issue of amiloride concentration in the study by Guan et al is an important issue in regards to specificity of action. Guan et al found a significant loss in myogenic control of afferent arteriolar diameter when the kidney was superfused with 10 μmol/L amiloride, a concentration slightly higher than desirable. However, a lower concentration of amiloride (5 μmol/L) produced a similar inhibitory effect when amiloride was placed in the blood-perfusate. Notably, the same concentration (5 μmol/L) has also been shown to specifically inhibit myogenic constriction in isolated mouse interlobar artery segments. The higher amiloride concentrations required with superfusion are likely attributable to diffusion barrier presented by tissue. Thus, the findings of the current investigation by Guan et al support a role for ENaC proteins in afferent arteriole myogenic constriction.

The findings of Guan et al, in conjunction with previous findings, suggest ENaC proteins can regulate myogenic constriction. However, further studies are required to determine whether ENaC proteins can alter myogenic constriction enough to regulate renal vascular resistance. Amiloride and its analogs have been useful for initial in vitro experiments, though they are not likely to be useful in future studies for several reasons. First, these agents can be “dirty,” and their use casts a shadow of doubt. Second, subunit specific analogs are not available, so the importance of specific degenerin proteins cannot be determined. Third, delivering enough amiloride (orally or intravenously) to achieve a vascular effect without a tubular effect (ie, diuresis) is not yet feasible. Thus, future studies will require gene-specific targeting to understand the importance of individual ENaC and ASIC proteins in afferent arteriolar myogenic constriction. Understanding how vascular ENaC and ASIC proteins are regulated may help prevent renal injury associated with renal disease and hypertension. Hopefully, it won’t require another 100 years.

Sources of Funding

This work was supported by a National Institutes of Health grant HL086996.

Disclosures

None.

References


Figure. A, Mechanosensor model. The mechanosensor model is a multimeric channel complex that includes extracellular matrix, cytoskeleton, and associated extracellular and intracellular linking proteins. Mammalian members of the degenerin family (ENaC and ASIC proteins) are predicted to form the ion-conducting pore. B, Speculative role of ENaC as mechanosensor in VSMCs. Mechanosensitive ion channel complexes containing ENaC or ASIC proteins may be activated by pressure-induced wall tension/stretch leading to Na⁺/Ca²⁺ entry. In turn, this ion influx leads to membrane depolarization, activation of L-type Ca²⁺ channels, and VSMC contraction.
Yes, No, Maybe So: ENaC Proteins as Mediators of Renal Myogenic Constriction
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Hypertension. 2009;54:962-963; originally published online August 31, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.139014

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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