The (F)low Down on the Endothelial Epithelial Sodium Channel

Epithelial Sodium Channel as a Brake on Flow-Mediated Vasodilation

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The epithelial sodium channel (ENaC) contributes to blood pressure homeostasis through renal salt and water transport; increases in ENaC activity increase salt and water reabsorption along the distal nephron, increasing extracellular fluid volume and blood pressure. The importance of tubular ENaC in cardiovascular homeostasis is manifested in Liddle’s disease and type I pseudohypoaldosteronism, diseases associated with the gain and loss of ENaC function, respectively. However, several recent studies suggest that ENaC proteins may play a more ubiquitous role in blood pressures associated with the gain and loss of ENaC function, respectively. ENaC proteins in the nephrotic syndrome are closely related to a family of mechanosensitive proteins in the nematode termed “degenerin;” several laboratories have characterized the potential role of ENaC proteins as mechanosensors.1–3 In addition to their role in salt and water homeostasis, ENaC proteins and their relatives, acid-sensing ion channels (ASICs), may contribute to control of blood pressure through reflex regulation of the autonomic nervous system (baroreflex, chemoreflex, and metaboreflex) and local control of vascular tone.1 Recent literature reviews suggest that ENaC proteins may function as sensors of pressure-induced vascular stretch and laminar flow.1–3 The role of ENaC as a mediator of pressure-induced constriction in certain vessels is supported by several investigations; however, the role of ENaC as a flow sensor remains unclear.1

ENaC as an Endothelial Flow Sensor

Because of their evolutionary relationship to mechanotransduction in the nematode, several laboratories have suggested that ENaC channels may act as flow sensors.2,3 Several lines of evidence suggest that ENaC channels are activated by flow. First, increases in laminar flow increase ENaC-dependent Na⁺ transport in the distal collecting duct. Second, laminar flow increases ENaC whole-cell current and channel open probability in oocytes expressing ENaC channels. Third, laminar flow increases the open-probability ENaC channels in endothelial cells.4 These studies suggest that ENaC channel activity can be regulated by laminar flow and, thus, that ENaC channels are candidates for transducing shear force in endothelial cells; however, the functional significance of ENaC in flow-mediated vascular reactivity is not clear.

The current report by Pérez et al5 demonstrates that ENaC expression in mesenteric endothelial cells regulates vascular tone. ENaC inhibition with amiloride (0.5 μmol/L) and benzamil (1 μmol/L) blunts agonist-induced vasoconstriction in an NO-dependent manner and increases NO production, a finding that suggests that basal ENaC activity in endothelial cells maintains vasoconstrictor reactivity by suppressing NO production (Figure). Furthermore, ENaC inhibition enhanced flow-mediated vasodilation, demonstrated by an upward shift of the flow-diameter relationship (Figure 7C in Reference 5), suggesting that basal-level ENaC activity acts as a brake on flow-mediated vasodilation in mesenteric arteries (resting diameter: ≈200 μm). The findings by Pérez et al5 demonstrate a functional role for endothelial ENaC in flow-mediated dilation but suggest that endothelial ENaC negatively modulates, but does not mediate, flow-mediated dilation in the mesenteric circulation.

Interpreting the importance of ENaC channels in this study is heavily dependent on the specificity of amiloride and its analogs. Although amiloride can block other channels and transporters, eg, voltage-gated Ca²⁺ and Na⁺ channels, Na⁺/H⁺ transporter, or the Na⁺/Ca²⁺ exchanger, amiloride can be highly selective for ENaC.6 The caveats are that the concentration must be submicromolar or very low micromolar. The study by Pérez et al5 used a submicromolar concentration of 0.5 μmol/L. Pérez et al5 also found a similar effect of benzamil, a lipophilic amiloride analog with increased selectivity for ENaC, and a lack of effect of ethyl isopropyl amiloride (0.5 μmol/L; Figure S2 in Reference 5), an amiloride analog selective for the Na⁺/H⁺ transporter. Thus, as far as we know, the doses of amiloride and benzamil used in the study by Pérez et al5 are relatively specific for ENaC. However, because there is no “silver bullet,” and lingering doubt regarding the amiloride specificity remains, future studies using alternative methods to inhibit ENaC expression, eg, transient gene silencing, and genetically modified animals are needed to confirm the results of Pérez et al.5

Although the findings of Pérez et al5 suggest that ENaC is probably not a flow sensor in mesenteric arteries, a direct role for ENaC as a mediator of flow-induced dilation in other circulatory beds cannot be ruled out. Heterogeneity in signaling mechanisms in vessels of different sizes and locations is common, particularly as it relates to the role of ENaC in vascular smooth muscle cells in mesenteric, renal, and cere-

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certain K^+ channels directly regulate ions that the closely related ASIC channels. ENaC proteins may interact with other ASIC proteins or putative endothelial mechanosensitive proteins (caveolin, integrins, etc) to form a multimeric flow-sensitive receptor complex that has altered amiloride sensitivity and more than Na^+.

Although these scenarios may seem unlikely, before we drive the stake into the heart of the “ENaCs-as-endothelial-flow-sensors” hypothesis, the role of ENaC proteins as endothelial flow sensors should be evaluated further using multiple approaches, including in vitro and whole-animal approaches in genetically modified animals.

An important finding of Pérez et al^5 is that this study provides evidence that the endothelial ENaC channels are active and participate in flow-induced dilation. Future studies are needed to define the role of ENaC channels as shear stress sensors in endothelial cells in mesenteric and other circulatory beds.

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**References**

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