Hypertension demands the integration and processing of a myriad of different input signals from a variety of sources. Regulation of central blood pressure is one such homeostatic system that depends critically on both volumetric and hemodynamic information. A common element for cardiovascular data transfer is sensing mechanical alterations such as cellular volume changes, changes in shear stresses, or changes in membrane tension or curvature. Stretch activation of membrane proteins, specifically ion channels, transduces hydrostatic pressure differences in the major blood vessels (via aortic and carotid baroreceptors) and small arteries and arterioles (via vascular smooth muscle cells [VSMCs]). Electrical signals from the baroreceptors travel via afferent nerves to integrative centers in the brain for processing, and appropriate efferent signals are generated to alter heart rate and peripheral resistance in a classic negative feedback loop. In contrast, there are important local autoregulatory control mechanisms that exist to alter blood flow in the capillary beds of the kidney, musculature, intestine, heart, and brain. These local effectors are also under central control to adjust peripheral vascular resistance when necessary. Presumptive mechanosensitive ion channels in VSMCs lining the arterioles are thought to subserve this function.

Until now, the identity of VSMC mechanosensitive channels was left to one’s musings. Wu and Davis reported a stretch-activated cation current in porcine coronary VSMCs. This current was blocked by hexamethonium and Grammostola spatulata venom, both of which are thought to block mechanosensitive channels. Göstehaneh et al established that amiloride-sensitive, epithelial Na⁺ channels (ENaCs) were expressed in a vascular endothelial cell line. The article by Drummond, Gebremedhin, and Harder strongly implicates members of the ENaC superfamily as playing a major role in VSMC mechanotransduction. By an impressive array of molecular biological, immunological, biochemical, and physiological techniques, they conclusively demonstrate that at least β-ENaC and γ-ENaC message and protein are present in rat VSMCs obtained from rat cerebral arterioles. Moreover, these investigators show that amiloride and benzamil, which are relatively high-affinity inhibitors of ENaC, effectively block the myogenic response (ie, stretch-induced vasoconstriction) of isolated and perfused rat brain arteries. However, Ditting et al concluded, on the basis of the inability of either amiloride or benzamid to block mechanically induced currents in rat cardiac ganglion nodosum cells, that ENaC is not an essential component of the cardiac mechanosensitive afferent reflex pathway.

Although individual ion channels have been shown to display characteristics consistent with being mechanosensitive, the channels responsible for mechanical transduction in most pressure-sensitive receptors (eg, inner ear hair cells, Pacinian corpuscles, baroreceptors) have not been, or are just starting to be, identified. For example, mechanical perturbations of membrane tension or shear have been shown to gate directly (ie, change the single-channel open probability) prokaryotic channels (MscL and MscS), Shaker potassium channels, N-type calcium channels, and ENaC. Before the report by Drummond et al, it was only in the arterial baroreceptor complex, inner ear hair cells, spider VS-3 slit-sense organ, dorsal root ganglion, osteoblasts, and in mammalian pain and touch receptors that any evidence concerning the molecular identification of components of ion channels that may subserve mechanosensation was proffered. Significantly, members of the degenerin (DEG)/ENaC superfamily surfaced in each of these systems.

The potential of ENaC and other family members to act as sensors of mechanical stress was first suggested in the initial cloning article of Canessa et al. Because of the high degree of amino acid homology between α-ENaC and the C. elegans proteins deg-1 and mec-4, proteins essential for touch sensitivity of the worm, Canessa et al (1993) believed that ENaC and the degenerins shared similar functions, especially controlling and sensing cellular volume. Yet, not everyone embraces the concept that DEG/ENaC are biological mechanosensors. Although definitive proof is not available, it is hard to ignore the fact that DEG/ENaC components routinely turn up in structures designed to sense mechanical perturbations.

So then, what is the mechanism of mechanotransduction? How does a change in mechanical stress gate ENaC or any other mechanosensitive ion channel? Hamill and Martinac summarized 3 possibilities: (1) bilayer tension or curvature directly activating a channel; (2) release of another molecule from a cell that in turn activates the channel; and (3) a tethering mechanism in which the ion channel binds either to the cytoskeleton or the extracellular matrix. Any movement of this network, say by a cell volume change or a direct mechanical force distorting the shape of the membrane, would “stress” the structure and hence gate the channel.

The opinions expressed in this editorial commentary are not necessarily those of the editors or of the American Heart Association.

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Hypertension is available at http://www.hypertensionaha.org
DOI: 10.1161/01.HYP.0000144467.43205.ed
Evidence exists to support all 3 mechanisms, especially for ENaC. Most investigators favor a tethered model, but mechanosensitive properties can also be attributed to ENaC, MscL, MscS, and even gramicidin when these channels are studied devoid of any apparent attachments. The reader is referred to an article by Morris and Homann for a wonderfully lucid discussion of lipid bilayer versus cytoskeleton contributions to membrane tension.

The work of Drummond et al. does leave some important questions unanswered. One such question is: What is the composition of the functional mechanosensitive channel in VSMC? Although β-ENaC and γ-ENaC were identified, α-ENaC was not. α-ENaC is the core subunit of the channel because β-ENaC and γ-ENaC, alone or in combination, cannot form a functional unit. However, Drummond et al. did not probe for other family members, such as acid-sensing ion channels or δ-ENaC; these can easily combine with β-ENaC and γ-ENaC to form functional channels. Regardless, if anyone doubts the power of mechanosensation on the cardiovascular system, consider this (inspired by Shakespeare’s 

“O, pity,” gan she cry. “Flint-hearted boy! ‘Tis but a kiss I beg, why art thou coy? Touch but my lips with those fair lips of thine – And my blood pressure shall rise, like leaves of a vine. My skin shall flush with the color of love. My heart shall pound, like the wings of a dove. My head shall throb with pulsatile flow. And serenity shall vanish, like an elusive doe.”

Fortunately, this work by Drummond et al. provides us with the beginnings of a mechanistic understanding of the first step of this youthfu l fascinated.

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Dale J. Benos

Hypertension. 2004;44:616-617; originally published online September 20, 2004;
doi: 10.1161/01.HYP.0000144467.43205.ed

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/44/5/616

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