Editorial

Two ways to feel the pressure: an endothelial Ca\textsuperscript{2+} entry channel with dual mechanosensitivity

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Abstract

One impressive function of the vascular endothelium is its ability to adjust the release of vasoactive mediators such as NO and PGI\textsubscript{2} almost instantaneously to changes in blood flow or blood pressure. Besides this fast feedback response to hemodynamic alterations, the endothelium is subject to long-term adaptations that are crucial for prevention of pathological processes such as atherogenesis. Among the various signals that are sensed by endothelial cells, mechanical forces which arise from pulsatile blood flow are probably most important for fast as well as long-term control of blood vessel function by the endothelium.

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See article by Brakemeier et al. [1] (pages 209–218) in this issue.

In this issue of Cardiovascular Research, Brakemeier et al. [1] report on a slow and long-lasting regulation by shear stress of an endothelial cation channel that is considered a primary mechanosensor for in-plane membrane tension (stretch). This Ca\textsuperscript{2+} permeable cation channel may represent a dual mechanosensor which serves both rapid and sustained, adaptive conversion of mechanical input signals into output signals such as formation of NO or PGI\textsubscript{2}. Primary sensing of flow-induced shear stress and stretch by the described cation channel involves two distinctly different principles of channel regulation. Acute in-plane membrane stretching activates the channel instantaneously, most likely due to a direct mechanosensitivity of the channel protein, while sustained shear stress is sensed by the channel via an additional slow process that involves protein phosphorylation.

1. Regulatory protein phosphorylation is a key event in immediate and long-term adaptive responses of the endothelium

Protein phosphorylation has long been recognized as a key event in immediate responses to mechanical stress such as enhanced nitric oxide formation [2], as well as in more sustained stress responses such as altered gene expression and rearrangement of the cytoskeleton [3]. Using the protein kinase inhibitors genistein and H-7, Brakemeier and colleagues [1] employed a classical pharmacological approach to test for involvement of protein kinases in the observed sustained up-regulation of the stretch-sensitive channels. It is reported that long-term regulation of stretch-sensitive channels by flow-induced tangential forces is suppressed by either of these two protein kinase inhibitors. The results do not allow for identification of the involved stress-regulated protein kinases, but support the concept that endothelial mechanotransduction involves a cascade of regulatory phosphorylations with protein tyrosin phosphorylation as a key event [4]. Recently, shear stress-induced translocation of signaling proteins to caveolae and caveolae-associated fast activation of the Ras–Raf–mitogen-activated protein

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(MAP) kinase pathway has been reported [5]. Thus, important proximal (membrane-associated) steps in mechanotransduction may take place in caveolin-rich lipid microdomains which provide the platform for effective interaction between signaling proteins. Among the serine/threonine kinases that have been implicated in mechanoadaptation of endothelial cells, the MAP kinases ERK1/ERK2 as well as protein kinase C species, which may serve as an upstream mediator of ERK1/ERK2 activation [6], appear as most important for blood flow-induced control of gene expression as well as cytoskeletal architecture [2,3,7], and may well be involved in modulation of ion channel functions.

It is of note that proximal mechanosensors which initiate the cascade of regulatory protein phosphorylations leading to endothelial adaptive responses are not yet clearly identified. In principle, small GTPases [8], enzymes such as phospholipase C [9] as well as cation channels are considered as such proximal mechanotransducers. Cation channels notorious in initiation and/or modulation of phosphorylation/dephosphorylation events via generation of local Ca$^{2+}$ and/or Na$^{+}$ gradients, and specific tyrosine kinases that have been implicated in the shear stress response are Ca$^{2+}$ dependent [10]. Interestingly, ERK1/ERK2 pathway has recently been reported to be sensitive to inhibition by Na$^{+}$ entry [11]. Moreover, Na$^{+}$ entry has been demonstrated to produce local Ca$^{2+}$ gradients at endothelial caveolae due to Na$^{+}$/Ca$^{2+}$ exchange [12]. Thus, constantly enhanced cation entry into endothelial cells may well trigger long-term, phosphorylation-mediated adaptations in the endothelium. Assuming that stretch-sensitive channels are activated not only by in-plane membrane tension as created by micropipette aspiration, but to some extent also by stretch components generated by experimental shear stress, it remains to be clarified whether the described sustained up-regulation of these cation channels represents a mechanism of Ca$^{2+}$- or Na$^{+}$-mediated positive autoregulation of these channels.

### 2. Phosphorylation-dependent up-regulation of mechanosensitive channels

Shear stress-induced, sustained facilitation of stretch-activated cation currents was found to be based on both an increase in the number of active channels in membrane patches as well as on increased mechanosensitivity. Increased density of active channels in membrane patches may result from either enhanced expression and/or enhanced insertion of channel proteins into the plasma membrane. Alternatively, also a promotion of channel clustering may be considered as the basis of the observed increase in channel density. The molecular target of the regulatory phosphorylation that results in sustained up-regulation of stretch-activated channels is elusive. Nonetheless, it is tempting to speculate about regulatory phosphorylation of the stretch-sensitive channel protein itself or of components of the membrane cytoskeleton which has been recognized as a crucial determinant of proximal mechanosensors.

Fig. 1. Hypothetical model of a dual mechanosensitive cation channel (SAC) which is subject to rapid regulation by stretch and sustained regulation by shear stress. The channel may be linked to flow-induced phosphorylation events in terms of a proximal regulator and/or a target of protein kinases.
Fig. 1 summarizes the concept that is put forward by the results of Brakemeier et al. A specific nonselective cation channels is able to transduce the two distinct physical stimuli, shear stress and in-plane tension, into local intracellular \( \text{Ca}^{2+} \) signals. The channel is subject to a distinct long-term adaptation which involves regulatory phosphorylation and appears therefore as a key element of mechanotransduction which allows for integration of multiple input signals and effective fine tuning of endothelial-dependent vasoregulation. The dual mechanosensitive cation channel is considered to govern vascular endothelial functions in two time domains, being critically involved in both fast and sustained adaptive responses. These properties make the described endothelial cation channel a most attractive target for novel therapeutic strategies.

References