Shear stress and intermediate-conductance calcium-activated potassium channels

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Received 29 September 2003; accepted 6 October 2003

See article by Brakemeier et al. [4] (pages 488–496) in this issue.

1. Introduction

Vascular endothelial cells (EC) are continuously exposed to shear stress associated with the flowing blood. Over the years, it has become clear that such shear exerts a multitude of effects on endothelial biology and vascular function and structure, ranging in time span from seconds to months. On the scale of seconds, shear-dependent vasodilation has been demonstrated in many experimental settings. In the course of months, shear stress is believed to shape the vascular bed through remodeling [1]. Thus, shear stress sensing provides a mechanistic base for the notion of Murray in 1926 that vascular diameter should be proportional to the cube of the carried flow in order to minimize the costs of maintaining a circulation [2]. Steady laminar shear is atheroprotective while low shear levels and temporal or spatial variation of shear have been related to development of atherosclerosis [3]. Considering the clear importance of shear stress, much research is devoted to identifying the mechanisms of shear stress sensing, the intracellular processes that occur in response to altered shear stress patterns, and the functional and structural consequences. The paper by Brakemeier et al., in this issue [4], shows that expression of intermediate-conductance calcium-activated potassium channel in human umbilical vein endothelial cells (HUVECs) is upregulated by arterial shear stress. The authors suggest that such upregulation could form a mechanism for long-term adaptation of endothelial cells to altered blood flow [4].

2. Intermediate-conductance calcium-activated potassium (IKCa) channels in EC

Endothelial cells express a vast array of ion channels [5]. Potassium channels in ECs include ATP-sensitive, inwardly rectifying, and Ca$^{2+}$-activated channels. The latter group of channels is activated by a rise in local intracellular calcium. They include large-, intermediate-, and small-conductance channels (BKCa, IKCa, and SKCa, respectively). IKCa channels have a single channel conductance of 15 pS in normal concentrations of extracellular K$^+$ [5]. The channels have a calmodulin binding site that is responsible for their calcium sensitivity. The channels are blocked by charybdotoxin and clotrimazole, but not by apamin (which blocks SKCa) or iberiotoxin (a blocker of BKCa) [6]. Recently, a structural analogue of clotrimazole, TRAM-34, has been developed as a selective blocker for IKCa channels [7]. 1-EBIO is an effective and more or less selective opener for IKCa channels [8].

3. Upregulation of IKCa channels by shear stress

The genes coding for IKCa and SKCa channels comprise four members, KCNN1–KCNN4; the article by Brakemeier studies expression of the KCNN4 (IKCa1) gene [9]. The authors observed that in HUVECs, 15 dyn/cm$^2$, reflecting arterial levels of shear stress, causes an eight-fold upregulation of IKCa1 mRNA after 4 h, which persisted at four-fold baseline levels after 24 h of shear. At lower shear levels (5 dyn/cm$^2$), IKCa1 upregulation occurred after 24 h. The persistence of upregulation suggests that this is a true adaptation process to increased shear stress, as also found for eNOS [10], rather than an ‘activation’ response such as upregulation of the adhesion molecule ICAM-1. Importantly, the authors also show the functional consequences of shear-induced IKCa1 upregulation. Thus, in whole-cell
patch-clamp experiments, $\text{IK}_\text{Ca}$ currents in response to $\text{Ca}^{2+}$ dialysis increased strongly after culture under shear. In addition, confluent HUVEC monolayers grown under shear had similar membrane potentials as their static controls, but hyperpolarizing responses to the endothelium-dependent dilator ATP and to the $\text{IK}_\text{Ca}$ opener 1-EBIO were strongly enhanced in the cells grown under shear. The authors finally show the involvement of the MEK/ERK pathway in the upregulation of $\text{IK}_\text{Ca}1$.

4. Role of $\text{IK}_\text{Ca}$ channels in endothelium-dependent dilation

The importance of potassium channels in general for endothelial function relates partly to calcium signaling and subsequent production of endothelium-derived factors [11]. Opening of potassium channels causes hyperpolarization and thus increases the driving force for calcium entry. This leads to a rise in intracellular calcium provided that pathways for calcium entry are simultaneously open. On the other hand, calcium-activated potassium channels act downstream of a rise in endothelial calcium. In particular, endothelial $\text{IK}_\text{Ca}$ and $\text{SK}_\text{Ca}$ channels have been implicated in endothelium-derived hyperpolarizing factor (EDHF)-mediated dilation [12–14]. Thus, an elevation of endothelial calcium causes opening of these channels, a rise in extracellular potassium in the space between EC and SMC, and subsequent opening of inward rectifying potassium channels and hyperpolarization of the SMC [15]. Alternatively, it has been suggested that the endothelial hyperpolarization can be transmitted directly to the SMC through gap junctions between EC and SMC [16,17]. Through either of these mechanisms, the observed upregulation of $\text{IK}_\text{Ca}$ channels under shear would contribute to a larger EDHF response in EC preconditioned to arterial shear levels.

There is no evidence that $\text{IK}_\text{Ca}$ channels act as primary shear sensors. Rather, these channels could participate in an EDHF pathway downstream from the shear stimulus. One could question what the function would be of shear stress upregulating its own signaling system in endothelial cells. Part of this may relate to the lack of NO bio-availability in many cardiovascular pathologies [18]. A lack of NO-dependent shear-induced vasodilation would cause deeper constriction and inward remodeling. This would increase shear stress, which is inversely proportional to the cube of the vessel diameter. Upregulation of eNOS and $\text{IK}_\text{Ca}$ channels would then allow the cell to respectively produce more NO and increase the contribution of NO-independent dilator pathways such as $\text{IK}_\text{Ca}$-driven EDHF, thereby restoring the cell’s shear stress sensitivity and normalizing diameter and shear stress. Indeed, strong EDHF contributions to flow-dependent dilation have been observed in eNOS knockout mice [19] and diseased human coronary vessels [20].

5. HUVECs as models for shear stress studies

The study by Brakemeier et al. [4] was performed on HUVECs, grown in a cone-and-plate viscometer. HUVECs form a convenient and widely used source of human endothelial cells, and much has been learned and can still be learned from this cell type. It makes sense to study the effects of arterial shear stress levels on phenotype of these venous cells for two reasons. Specifically, it may provide information on the adaptation processes in venous bypass grafts. In a broader perspective, such studies help in understanding the contribution of disturbed shear stress profiles to local endothelial dysfunction and atherosclerosis. The paper by Brakemeier et al. makes an important contribution to this field of research. However, future work will be required to establish whether the currently found upregulation of $\text{IK}_\text{Ca}1$ under shear also occurs in arterial EC, and whether arterial and venous EC differ in their basal expression levels of this channel.

References


