Endothelin enhances activity of mechanosensitive channels: A mechanism for ET augmentation of the myogenic response

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That stretching smooth muscle can result in contraction has been appreciated for over a hundred years (see [1]), and Bayliss in 1902 [1] demonstrated that an increase in luminal pressure in arteries resulted in passive distension followed by constriction. Neural and hormonal mechanisms were excluded, so mechanisms intrinsic to smooth muscle were invoked to explain this phenomenon, now known as the myogenic response. Reports of stretch-induced activation of depolarization [2] and action potentials [3] in visceral smooth muscle were followed by studies on blood vessels in which increases in luminal pressure were associated with depolarization [4–6] and the initiation of action potentials [4]. Attenuation of the myogenic constriction by Ca2+-channel blockers implicated voltage-operated Ca2+ channels. But what causes the critical depolarization that activates the Ca2+ channels? In a wide range of cell types, including vascular smooth muscle [7], negative pressure applied to patch-clamp electrodes activates various ion channels, particularly poorly selective cation channels. Thus, pressurization of blood vessels stretches their walls which activates stretch-sensitive cation channels, resulting in depolarization that activates voltage-operated Ca2+ channels, and the ensuing influx of Ca2+ initiates constriction. However, additional dimensions add complexity and raise further questions. These are generally centred on the processes that underlie stretch activation of ion channels, the role of the intracellular and extracellular structural elements (cytoskeleton, integrins, and extracellular matrix (ECM)), and the role and contribution of second messenger pathways. These are all likely to be integrally involved in the overall process of the myogenic response.

Physiologically, the myogenic response functions in an autoregulatory manner to help maintain appropriate tissue perfusion despite changes in blood pressure. However, some diseases are associated with an enhanced myogenic response, and in hypertension, at least part of this enhancement has been attributed to the release of vasoconstrictors, particularly endothelin-1 (ET) [8,9]. ET activates the phospholipase C-diacylglycerol-protein kinase C (PKC), and Rho–Rho kinase pathways. ET can also evoke depolarization through the activation of several types of Ca2+-permeable poorly selective cation channels [10]. Ca2+ influx through the cation channels and through depolarization-activated Ca2+ channels contributes to constriction. Additionally, activation of PKC and Rho kinase can increase the sensitivity of the contractile apparatus to Ca2+, which results in greater constriction per unit rise in Ca2+ and can result in a relatively slow constriction in the absence of any increase in cytoplasmic free Ca2+.

In this issue, Lee et al. [11] report a new link between two major constricting influences in blood vessels – the myogenic response and ET – in which the sensitivity of mechanosensitive cation channels to stretch is increased by ET via PKC. Single channel currents were recorded in cell-attached mode from smooth muscle cells isolated from rabbit pulmonary and cerebral arteries. Negative pressure applied to patch electrodes activated mechanosensitive channels, and in the presence of ET, greater channel activity occurred for the same mechanical stimulus. This suggests a mechanism whereby ET could enhance the myogenic response. Importantly, Lee et al. confirmed this possibility by studying the myogenic response in pressurized segments of cerebral arteries. Additional mechanisms likely contribute to ET enhancement of the
myogenic response, particularly sensitization of the contractile apparatus to Ca\(^{2+}\), but were not explored in this study.

Lee et al. not only provide answers to some questions, but also raise others, of which the particular channel type involved is a strident issue. Although ET can activate poorly selective cation channels, in their study this did not occur, likely due to the particular experimental conditions that ensured Ca\(^{2+}\)-free conditions (0 Ca\(^{2+}\) plus 2 mM EGTA, both sides of the membrane, from 30 min before recording). Although the ET-activatable channels cannot be definitively ruled out, the involvement of another type of cation channel was proposed which is blocked by GsMTx-4, a peptide that blocks a widely occurring mechanosensitive cation channel. GsMTx-4 also inhibited the myogenic response in pressurized vessels. Thus, these results indicate that the mechanical sensitivity of this GsMTx-4-blockable mechanosensitive cation channel can be modulated by the ET/PKC pathway and can thereby contribute to the ET-enhancement of the myogenic response.

There are two main types of poorly selective cation channels that are mechanosensitive: 1) Degrenerin/epithelial Na\(^+\) channels (ENaC) likely contribute to the myogenic response in at least some arteries, since siRNA knockdown of the \(\beta\)- and \(\gamma\)-ENaC proteins inhibits the myogenic response [12]; 2) Of the transient receptor potential (TRP) channels, TRPC6 channels have been implicated through antisense oligonucleotide knockdown of the channels and the myogenic response [13]. These channels are blocked by GsMTx-4, but unlike the channels studied by Lee et al., TRPC6 channels appear to be inhibited by PKC (see [14]). TRPM4 channels have also been implicated in the myogenic response through antisense studies, but unlike the channels of Lee et al., they are activated by cytoplasmic Ca\(^{2+}\), and this Ca\(^{2+}\) sensitivity is increased by PKC [14]. TRPC1 channels are also mechanosensitive [15] and occur in smooth muscle, but their role in the myogenic response has yet to be tested. It is thus difficult to relate the mechanosensitive channels in the study by Lee et al. to the likely candidates already implicated in the myogenic response. It would be interesting to determine the effects of GsMTx-4 on the ET-activatable cation channels to better gauge their possible involvement.

Another major issue is how the mechanical force of luminal pressure is translated into activation of mechanosensitive channels. The ECM, cytoskeleton, and integrins provide a structural framework by which mechanical forces can be transferred to cellular components. The result can be the activation of various messenger systems (e.g. focal adhesion kinase, phospholipase A\(_2\), tyrosine phosphorylation, Rhoa/Rho kinase, MAP kinases, heat shock proteins, various isoforms of PKC), which could activate mechanosensitive ion channels in an indirect manner. Mechanical activity could also be transferred directly to the channels via cytoskeletal attachments. Changes in the contractile state of structural elements, such as through their Ca\(^{2+}\) sensitivity, or the state of actin polymerization, could be means by which the sensitivity of mechanosensitive channels to stretch is modulated. Stretch can also affect the activity of some ion channels via direct effects on the membrane bilayer. Since the ECM and the myogenic response are modified in some diseases, an interesting question that has received scant attention is to what extent the sensitivity of mechanosensitive ion channels is altered by such structural changes and thereby contributes to disease-altered myogenic responses.

Clearly, much progress has been made towards a better understanding of mechanisms underlying Bayliss’ observations, but their relative contributions are far from clear and many details still remain unresolved. The involvement of the various mechanisms and the implications for pathophysiological conditions provide therapeutic potential and need further exploration.

References