Ion channel dysfunction in endothelium dependent regulation of vascular smooth muscle

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The endothelium plays a major role in determining blood vessel calibre and hence tissue blood flow. Nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF) contribute to vasodilation, the latter being particularly prominent in small blood vessels. Endothelial dysfunction is a prominent feature of and may even be a very early contributor to the pathology of many vascular diseases, for example, hypertension, atherosclerosis, pre-eclampsia and the inevitable vascular complications of diabetes. NO is an important vasodilator that draws on diverse mechanisms to achieve vascular smooth muscle dilation. NO may reduce cytoplasmic Ca^{2+} by stimulating extrusion mechanisms and suppress Ca^{2+} influx by hyperpolarizing the smooth muscle cell. However, perhaps the most important action of NO is to decrease the sensitivity of the contractile apparatus to Ca^{2+}. Its reactive nature renders NO particularly vulnerable to attack by free radicals, whose levels are elevated in obesity and in diseases such as diabetes.

Oxidative stress can reduce the production and bioavailability of NO. This means that endothelium dependent vasodilation falls increasingly to mechanisms such as EDHF when the bioavailability of NO is impaired. As its name suggests, vascular smooth muscle hyperpolarization is the hallmark of and essential to EDHF vasodilation, and hence ion channels are central to its action. Endothelial cells possess intermediate- and small-conductance, Ca^{2+}-activated K^+ (IK_{Ca} and SK_{Ca}) channels and these are essential for the generation of the response that gives rise to EDHF in the smooth muscle. Apart from this, there is lack of consensus regarding the mechanism(s) mediating EDHF.

One thing is clear; EDHF is not a single entity, the same in all vessels throughout the body, and in every species. Rather, endothelial-derived smooth muscle hyperpolarization can be brought about by many different mechanisms. These include the release from the endothelium of one or more of a range of substances that act on the smooth muscle to open K^+ channels and/or stimulate electrogenic ion pumps in some vascular beds. Cytochrome P450 metabolites of arachidonic acid are prominent in this role and these activate smooth muscle large-conductance K (BK_{Ca}) channels that give rise to EDHF. The density of these ion channels is markedly reduced in a rat model of type 2 diabetes. An increase in extracellular K^+ resulting from the opening of endothelial IK_{Ca} and SK_{Ca} channels has also been implicated as another diffusible EDHF. This K^+ induces smooth muscle hyperpolarization by stimulating inwardly rectifying K^+ channels and the Na^+/K^+ ATPase. This mechanism appears to be impaired in the classical streptozotocin (STZ) rat model of type 1 diabetes. Impairment of Na^+/K^+ ATPase function has also been reported in the forearm vessels of humans with hypertension.

Alternatively, smooth muscle hyperpolarization may result from the electronic spread, via myoendothelial gap junctions (MEGJs), of the hyperpolarization generated by SK_{Ca} and IK_{Ca} channels in the endothelial cells. Furthermore, cyclic AMP may facilitate spread of current through MEGJs. We have recently found that the contributions of both SK_{Ca} and IK_{Ca} channels to EDHF-mediated responses are reduced both *in vitro* and *in vivo* in mesenteric artery of STZ diabetic rats. MEGJ patency remained intact. In contrast, in a rat model of obesity-linked, type 2 diabetes, there is a reduction in the expression of gap junction proteins. More recent studies have suggested the possibility that more than one mechanism of EDHF can act in concert in the one artery.

In conclusion, ion channels play an important role in endothelium dependent vasodilation and are particularly prominent in the EDHF response, which assumes increasing importance as vessel size decreases. Although it was initially suggested that EDHF might step in to compensate when NO bioavailability is reduced, it is now evident that the EDHF mechanism itself may also be compromised in vascular disease, sometimes to a greater extent than NO. EDHF is reduced in human hypertension, diabetes, pre-eclampsia, and in animal models of these diseases. Ion channel dysfunction at the level of the endothelium and smooth muscle contributes to this.