Endothelium-dependent vasodilatation: Fundamental role of SK_{Ca} and IK_{Ca} potassium channels

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Activation of vascular potassium (K) channels underlies both the radial and axial spread of dilatation within the artery wall. Radial spread, or an endothelium-dependent hyperpolarizing factor (EDHF) response, is initiated by agonist activation of endothelial cells, while axial, or spreading dilatation, can follow local hyperpolarization in either the endothelial or the smooth muscle cells.

EDHF describes the endothelium dependent smooth muscle hyperpolarization persisting in the presence of inhibitors of nitric oxide (NO) synthase and cyclooxygenase, and causes smooth muscle relaxation by closing voltage-operated calcium channels. Originally assumed to reflect the action of a diffusible factor or factors, with analogy to EDRF or NO, the term is now also taken to encompass the possibility of passive spread of hyperpolarization from the endothelium (Busse *et al.*, 2002). Key to understanding this pathway is the observation that EDHF-evoked hyperpolarization and associated smooth muscle relaxation can be blocked with a combination of apamin (blocks small conductance calcium-activated K channels, SK_{Ca}) and charybdotoxin (blocks intermediate and large calcium-activated K channels, IK_{Ca} and BK_{Ca}, plus delayed rectifier channels, K_V). Alone, these toxins partially blocked EDHF responses, but in combination they totally abolished the response. Although initially taken to indicate that SK_{Ca} and BK_{Ca} on the smooth muscle were responsible for hyperpolarization (to a diffusible EDHF), iberiotoxin was unable to substitute for charybdotoxin (see Busse *et al.*, 2002 for review). Furthermore, direct membrane potential measurements from endothelial cells *in situ* revealed that apamin and charybdotoxin are acting on K channels in these cells (Edwards *et al.*, 1998). Pharmacological studies (using 1-EBIO and TRAM-34/39) then showed that the target for charybdotoxin is in fact the IK_{Ca} channel. Thus, agonist activation of the endothelium, leading to increases in $[Ca^{2+}]_i$, activates both SK_{Ca} and IK_{Ca} (which may be spatially separated, Crane *et al.*, 2003) causing hyperpolarization which is transfered by a diffusible factor or passive spread through myoendothelial gap junctions to the adjacent smooth muscle, where relaxation is evoked.

In addition to radial spread, axial spread of hyperpolarization is well described in the microcirculation (see Segal 2005). However, it seems to reflect an inherent property of resistance arteries as well (Takano *et al.*, 2004). In small mesenteric arteries, selective activation of endothelial cell hyperpolarization, or of the K_{ATP} channels localized in the smooth muscle, results in hyperpolarization which spreads along the endothelium causing distant upstream dilatation. Interestingly, spread of hyperpoarization is not associated with an increase in endotheial cell $[Ca^{2+}]$ (Takano, 2004). It also may in part reflect K_{IR} activity (Goto *et al.*, 2004).

Vascular potassium channels therefore play a crucial role in the spread of dilator signals through the artery wall, and disruption of this role may underlie alterations in vascular function in cardiovascular disease.

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