Endothelial potassium channels in the regulation of vascular tone in health and in disease

H.A. Coleman, M. Tare and H.C. Parkington, Department of Physiology, Monash University, Vic 3800, Australia.

Ionic mechanisms underlying EDHF. The elusive nature of endothelium-derived hyperpolarising factor (EDHF) has hampered detailed study of the underlying ionic mechanisms. By cutting arterioles into electrically short lengths it is possible to record membrane currents using single electrode voltage-clamp when the smooth muscle and endothelial cells remain in their normal functional relationship. Membrane potential can also be recorded simultaneously with contractile activity in these preparations. With this approach it is thus possible to study endothelial-dependent ionic mechanisms irrespective of the processes involved and to relate the currents to contractile activity.

In the presence of nitric oxide and prostaglandin synthesis inhibitors, acetylcholine (ACh) evoked hyperpolarisation and relaxation of guinea-pig submucosal arterioles which were abolished by the K^+ channel blockers charybdotoxin (ChTx) plus apamin. Under voltage-clamp, ACh evoked an outward current. ChTx reduced the amplitude, while apamin plus ChTx abolished the outward current. Subtraction of the currents revealed the ChTx- and apamin-sensitive currents and their separate current-voltage relationships. Both currents reversed near the expected K^+ equilibrium potential, were weakly outwardly rectifying, and displayed little, if any, time or voltage-dependent gating. The components have the biophysical and pharmacological characteristics of the intermediate- and small-conductance calcium-activated K^+ channels, IK_{Ca} and SK_{Ca}, respectively (Coleman *et al.*, 2001).

Myoendothelial electrical coupling. Electrotonic spread between endothelial and smooth muscle cells is an important consideration for EDHF. Smooth muscle specific responses recorded from dye-labelled endothelial cells were indistinguishable from those recorded from dye-labelled smooth muscle cells. In contrast, in rat femoral artery, in which the smooth muscle and endothelial layers are not coupled electrically, ACh evoked hyperpolarisation only in endothelial cells. This supports the idea that EDHF hyperpolarisation results from electrotonic spread from the endothelium to the smooth muscle (Coleman *et al.*, 2001; Sandow *et al.*, 2002).

EDHF *in vivo*. The functional significance of EDHF *in vivo* was addressed by the local infusion of ACh into the rat mesenteric vascular bed. With nitric oxide and prostaglandin synthesis blocked, ACh evoked increases in blood flow that were blocked with the local infusion of ChTx plus apamin. These results indicate that EDHF contributes to endothelium-dependent vasorelaxation *in vivo* (Parkington *et al.*, 2002).

EDHF in diabetes. Vasodilator dysfunction is a well established hallmark of diabetes. In arteries from diabetic rats and women, EDHF is diminished. This is not only associated with reduced EDHF hyperpolarisation in vascular smooth muscle, but is also associated with a reduced hyperpolarisation in the endothelial cells (Wigg *et al.*, 2001).

In conclusion, the most economical explanation for EDHF is that it arises from activation of IK_{Ca} and SK_{Ca} channels in endothelial cells. The resulting endothelial hyperpolarisation spreads via myoendothelial junctions to result in the EDHF-attributed hyperpolarisation in vascular smooth muscle cells. These processes contribute to endothelium-dependent vasodilation *in vivo* and their dysfunction contributes to the impairment of vascular regulation that occurs in diabetes.

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