Endothelium-derived hyperpolarising factor and cell coupling: Factors and fiction?

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Together with nitric oxide and prostaglandins, endothelium-derived hyperpolarising factor (EDHF) is one of three vasodilatory factors produced by the arterial endothelium. The nature and mechanism of action of EDHF is the subject of intense current research interest. EDHF activity has been reported to be dependent on either the release of a diffusible substance from the endothelium or to the direct contact of endothelial cells and smooth muscle cells via gap junctions. Diffusible factors proposed as EDHFs include K^+ ions, H_2O_2, epoxyeicosatrienoic acids, L-NAME insensitive nitric oxide, and C-type natriuretic peptide. Contact-mediated EDHF is dependent on myoendothelial gap junctions (MEGJs) that enable the passage of small molecules, and/or direct electrical coupling between the two cell layers. In the latter case, this coupling would result in an endothelial cell hyperpolarisation being directly transferred to the smooth muscle, for the subsequent generation of an arterial relaxation. This latter mechanism represents the simplest explanation of EDHF activity.

Interestingly, it has been shown that the nature and mechanism of action of EDHF can differ along and between vascular beds, and that it can also change during development and in ageing and disease. Furthemore, in the mesenteric vascular bed of the rat, EDHF has been described to be K^+ ions, H_2O_2, L-NAME insensitive nitric oxide, CNP, as well as to be due to the direct electrical coupling of endothelial cells and smooth muscle cells. This variation is likely to be due to methodological differences between the laboratories in which such studies were made. Thus, the debate in the EDHF field is often clouded by such unfortunately inconsistent reports.

Studies from our laboratory have focused on the potential role of MEGJs in EDHF activity. We have found that the distribution and activity of MEGJs is correlated with the presence of EDHF within and between vascular beds, during development and in disease. In smaller distal mesenteric arteries of the rat, for example, MEGJs are more prevalent than in larger proximal vessels (Sandow & Hill, 2000), in line with the EDHF-mediated relaxation being more prominent in the smaller than in the larger vessels (Shimokawa *et al.*, 1996). In this vascular bed, EDHF-mediated hyperpolarisation and the transfer of endothelial cell hyperpolarisation are correlated with the presence of MEGJs (Sandow *et al.*, 2002). Furthermore, in the femoral artery of the rat the lack of MEGJs is correlated with the absence EDHF-mediated hyperpolarisation (Sandow *et al.*, 2002). In the lateral saphenous artery of the juvenile rat, MEGJs are prevalent and EDHF-mediated hyperpolarisation and relaxation present (Sandow *et al.*, 2003a). This is in contrast to the saphenous artery of the adult, where MEGJs were rare and EDHF absent (Sandow *et al.*, 2003a). The relationship between EDHF and MEGJs is somewhat more complicated in disease states, such as in hypertension. In a comparative study of the caudal artery of the hypertensive SHR and normotensive WKY rat, EDHF activity was maintained, in spite of an increase in the number of smooth muscle cell layers in the vessels from the hypertensive rat. This maintenance was found to be due to a concomitant increase in the incidence of MEGJs in the caudal artery of the SHR rat (Sandow *et al.*, 2003b).

These studies demonstrate that there is a consistent positive correlation between MEGJs and EDHF activity, both of which show a heterogeneous distribution within and between vascular beds, during development and in disease. Thus, these studies demonstrate that heterocellular coupling can account for EDHF activity. Further studies will enable the identification of potential new therapeutic targets for the regional control of vasodilator function, vascular tone and cardiovascular disease.

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