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Themed Section: Vascular Endothelium in Health and Disease

# EDITORIAL

# The vascular endothelium: still amazing us 30 years on

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As pharmacology undergraduates, we both recall our lecturers' confident assertion that the vascular endothelium was nothing more than a slippery, inert monolayer, functioning to aid the non-turbulent flow of blood to the tissues. All this changed in the 1970s, largely with the discovery that angiotensin-converting enzyme (ACE) was located in vascular endothelial cells (Caldwell *et al.*, 1976). The importance of angiotensin II in blood pressure maintenance and the subsequent development of ACE inhibitors remain key factors in the control of essential hypertension in man.

Nothing, however, could have prepared the scientific community for the impact of the simple organ-bath experiments of Robert Furchgott at the end of that decade (Furchgott and Zawadzki, 1980). The ensuing 'EDRF story' has been reviewed many times, and in this *Themed Issue* of the *British Journal of Pharmacology* (*BJP*), the importance of this discovery is also highlighted but placed in context with more recent endothelial discoveries (Garland *et al.*, 2011a).

The purpose of this issue of the *BJP* is not to provide a forum for comprehensive reviews on all aspects of the pharmacology of the vascular endothelium. Instead, it presents a snapshot of some of the overviews originally presented in a symposium we organized for WorldPharma2010 in Copenhagen, together with original research papers with an endothelial theme.

For both of us, there have been many exciting general developments in the endothelial story over the past decade, but of these, two stand out. One is the increasing recognition of the relevance of *spreading or conducted vasodilatation*, the phenomenon whereby electrical signals generated at one locus in a blood vessel are able to spread significant distances along that vessel (irrespective of the direction of fluid flow) to influence contractility remote from the region of signal initiation. The discovery that catecholamines can activate this fundamental process via β-adrenoceptors can be found in this issue (Garland *et al.*, 2011b). The second key development in our understanding has been the recognition of the fundamental role of *microdomain signalling*, particularly in the functional responses initiated by the endothelium. With technical developments in imaging, microelectrodes and other means to study the mechanisms that underlie function in very small blood vessels, the amazing intra- and extra-cellular complexities of endothelial-myocyte interactions have begun to unravel. Of particular note has been the focus on microdomains within the endothelial cell projections that traverse holes in the internal elastic lamina. Such microdomains are of critical importance not only for the vascular extracellular calcium-sensing receptor (Smajilovic *et al.*, 2011), but also for the actions of endothelial cell NADPH oxidases (Wingler *et al.*, 2011) and gasotransmitters, such as $H_2S$ (Szabó and Papapetropoulos, 2011). Their relevance has been further highlighted since WorldPharma2010. Thus, in conditions such as hypertension, deficiencies in individual microdomain components may play a central role in the altered vascular responsiveness associated with the disease (Garland, 2010; Weston *et al.*, 2010).

Although the inhibitory effects of the endothelium on vascular tone continue to receive much attention, the production of endothelium-derived *contractile* factors (EDCFs) is also of vital importance. In this issue, Félétou *et al.* (2011) review this aspect of endothelium-mediated vasomotor control and particularly the roles played by the diverse products of cyclooxygenase enzymes in ageing and cardiovascular disorders.

The last article in this issue provides an additional dimension to the vascular endothelial cell story, with new findings

concerning the phenomenon of neurovascular coupling (Longden *et al.*, 2011). In cerebral blood vessels, astrocytic end-feet encircle cerebral arterioles, and, together with intravascular endothelial cells, form a diameter-controlling system of enormous complexity and subtlety. The similarities and differences between the types of $Ca^{2+}$ sensitive $K^+$ channel within the 'end-feet' and the vascular endothelial cells is fascinating when read in conjunction with the movies included in the paper's Appendix.

So, from small beginnings come great things. The use of the pharmacologists' tool of bioassay enabled Robert Furchgott's discovery of endothelial NO, and as a result, focused subsequent generations on the importance of this cellular monolayer. Technological developments have already allowed and continue to enable us to unravel the complex interactions between the endothelium and the rest of the cardiovascular system. While it is now clear that these interactions are a fundamental aspect of cardiovascular physiology and pathophysiology, there is surely much that remains to surprise and inform us!

## Acknowledgements

On a final, personal note, we both pay enormous tribute to two colleagues in our respective scientific lives. Without Kim Dora (CJG) and Gill Edwards (AHW), neither of us would be writing this Editorial. We also take this opportunity to acknowledge our continuing mutual friendship and respect. Through our many conversations and meetings and with the involvement of KD, GE and our many collaborators, our scientific discoveries have always been the source of enormous enjoyment, stimulation and fun.

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## Conflicts of interest

None.

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