

CORRESPONDENCE

EDHF and endothelial potassiun channels: IK_{Ca} and SK_{Ca}

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The paper entitled 'Selective blockade of endothelial Ca^{2+}-activated small and intermediate conductance K^+-channels suppresses EDHF-mediated responses' (by Eichler *et al.* (2003). *Br. J. Pharmacol.*, **138**, 594–601) nicely confirms that the activation of specific endothelial Ca^{2+}-activated potassium channels, respectively SK_{Ca} and IK_{Ca}, is an obligatory step in order to observe endothelium dependent hyperpolarization, that is, EDHF-mediated responses. The original contribution of this paper is the utilization of newly synthesized tools, namely TRAM-39 and TRAM-34, which selectively block IK_{Ca}, without inhibiting either BK_{Ca} or cyctochrome P450 (Wulff *et al.* (2000). *Proc. Natl. Acad. Sci. U.S.A.* **97**, 8151–8156). These studies are of importance as a great deal of confusion has arisen from the interpretation of the data obtained with charybdotoxin, which blocks IK_{Ca}, BK_{Ca}, and some K_V, as well as with clotrimazole, which blocks IK_{Ca} but also inhibits cytochrome *P*450. The elucidation of the mechanism involved in EDHF-mediated responses has been a very hot topic in recent years, and there is still a great deal of controversy in the scientific community about whether or not EDHF-mediated responses involve a diffusible factor and whether or not a cytochrome *P*450 metabolite could be this elusive factor. Hence, the study by Eichler *et al.* is both timely and appropriate and its publication in the *British Journal of Pharmacology*, the leading journal in publishing EDHF-related papers, was justified.

However, in this manuscript the historical background has been largely ignored. Thus, the key references to the studies that first proposed and then proved that EDHF-mediated responses require the specific activation of endothelial SK_{Ca} and IK_{Ca} (or similarly that the site of action of apamin and charybdotoxin was on the endothelial cells) are absent.

At least some of the following works should have been credited:

- Garland and Plane (*Endothelium-derived Hyperpolarizing Factor*. Harwood Academic Publishers, 1996, pp. 173–179): This was the first work to demonstrate that EDHF-mediated responses were inhibited by the combination of apamin plus charybdotoxin.
- Zygmunt and Höggestatt (*Br. J. Pharmacol.*, **117**, 1600–1606, 1996), Pettersson *et al.* (*Br. J. Pharmacol.*, **120**, 1344–1350, 1997), Zygmunt *et al.* (*Br. J. Pharmacol.*, **121**, 141–149, 1997), Chataigneau *et al.* (*Br. J. Pharmacol.*, **123**, 574–580, 1998), Quignard *et al.* (*Br. J. Pharmacol.*, **127**, 27–34, 1999). These papers show that iberiotoxin cannot mimic the effect of charybdotoxin, indicating that BK_{Ca} are not involved in most of the EDHF-mediated responses.
- Edwards *et al.* (*Nature*, **396**, 269–272, 1998), Ohashi *et al.* (*Br. J. Pharmacol.*, **126**, 19–26, 1999), Edwards *et al.* (*Br. J. Pharmacol.*, **129**, 1145–1162, 2000). These papers demonstrate that charybdotoxin and apamin act on the endothelial cells.
- Edwards *et al.* (*Br. J. Pharmacol.*, **128**, 1064–1070 and 1788–1794, 1999), Coleman *et al.* (*Am. J. Physiol.*, **280**, H2478–H2483, 2002). These papers show that 1-EBIO, an activator of IK_{Ca}, produced the hyperpolarization of the endothelial cells, the endothelium-dependent hyperpolarization of smooth muscle cells but not the direct hyperpolarization of the smooth muscle cells, effects that were inhibited by charybdotoxin but not by iberiotoxin. These results indicated that the activation of endothelial IK_{Ca} was partially mimicking the EDHF-mediated responses.
- Burnham *et al.* (*Br. J. Pharmacol.*, **135**, 1133–1143, 2002), Bychkov *et al.* (*Br. J. Pharmacol.*, **138**, 1346–1354, 2002). Based on electrophysiology (microelectrode and patch-clamp: whole-cell and single-channel recording and analysis), molecular biology (cloning, RT–PCR, Western blot), immunohistochemistry and pharmacology, these papers show that the apamin-sensitive SK_{Ca} containing the SK3 subunit and the charybdotoxin-sensitive, iberiotoxin-insensitive IK_{Ca} (IK_1 gene product) are expressed in endothelial cells and that these channels are likely to confer all or part of the apamin- and charybdotoxin-sensitive components of EDHF-mediated responses.
- The evidence that the EDHF-mediated responses were dependent on the activation of endothelial SK_{Ca} and IK_{Ca} was so strong that it was already mentioned in a review published by TiPS in August 2002 (Busse *et al.*, *Trends Pharmacol. Sci.*, **23**, 374–380, 2002).

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