

RESPONSE

Endothelial calcium-activated K^+-channels and EDHF signalling

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In recent years, good evidence has emerged that an elevation of intracellular $[Ca^{2+}]_i$ and subsequent activation of endothelial IK_{Ca} and SK_{Ca} inducing hyperpolarization are required for the initiation of EDHF-mediated responses (for review, see Busse *et al*., 2002). Thus, among the scientific community, there was already considerable opinion that besides other proposed mechanisms such as cytochrome *P*450 enzymes, the activation of these hyperpolarizing K_{Ca} channels in the endothelium is of pivotal importance for the generation of the EDHF signal in many vessels. However, in the past, the use of pharmacological tools, for example, ion channel modulators of weak or doubtful selectivity, might have hampered or even obscured the identification of the signal transduction mechanisms underlying EDHF-mediated vasodilatation. Thus, retrospectively, results from studies using pharmacological tools of low selectivity should be interpreted more cautiously. The purpose of our work was to use new selective pharmacological tools, that is, the highly selective IK_{Ca} inhibitors TRAM-34 and TRAM-39 (Wulff *et al*., 2000) to reveal the involvement of the endothelial IK_{Ca} in endothelial hyperpolarization and thus EDHF-mediated vasodilatation. Overall, we think that highly selective tools are needed to ascertain the involvement of a specific mechanism, especially when referring to the involvement of ion channels. Also, we agree that besides many other articles mentioned, the work of Garland & Plane (1996) demonstrating that a combination of apamin and charybdotoxin inhibits EDHF-mediated responses, as well as the article by Busse *et al*. (2002), reviewing the historical background, are credited as important contributions in the elucidation of mechanism of EDHF signaling.

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