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Endothelium-derived hyperpolarizing factor

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Keywords

EDHF, endothelium-derived hyperpolarizing factor, mice, nitric oxide, prostacyclin

Introduction

At least three different vasodilating agents are synthesized and released by the endothelium. Although the properties of NO and prostacyclin have been extensively investigated, the nature and mechanism of action of EDHF is still controversial. This paper characterizes EDHF-mediated responses using eNOS knockout mice.

Comments

Endothelium-derived hyperpolarizing factor (EDHF) was proposed more than 10 years ago. This was mainly because of observations that, in the presence of combined endothelial nitric oxide synthase (eNOS) and cyclo-oxygenase inhibition, classic endothelium-dependent vasodilators (such as acetylcholine [Ach] and bradykinin [BK]) still induce endothelium-dependent vasodilatation. Because the third endothelium-derived factor hyperpolarizes vascular smooth muscle cells, it was named EDHF. Controversy arose, when NO was shown to hyperpolarize smooth muscle cells. Another drawback for these studies was that they relied on the inhibitors used to completely suppress NOS and cyclo-oxygenase activity, which may not always be the case. This study completely excludes the participation of eNOS and NO in the EDHF-like dilation because identical results were obtained in wild-type and eNOS(-/-) mice. The exact nature of EDHF may not be completely revealed until the factor is isolated or chemically identified.

Methods

The authors compared the vasodilator responses to endothelium-dependent agonists, Ach, BK and the endothelium-independent vasodilator, sodium nitroprusside, *in vitro* and *in vivo*using wild-type and eNOS(-/-) mice.

Results

Baseline mean arterial pressure (MAP) was significantly lower in wild-type than in eNOS(-/-) mice. A combined diclofenac (cyclooxygenase inhibitor) and L-NAME (NOS inhibitor) treatment significantly increased MAP in wild-type, but slightly decreased MAP in eNOS(-/-) mice. *In vivo*, BK decreased MAP to an identical extent in wild-type and eNOS(-/-) mice, which was not affected by combined L-NAME and diclofenac treatment. Ach induced a concentration-dependent relaxation of isolated artery rings from wild-type, but not eNOS(-/-) mice. The Ach response was completely inhibited by L-NAME plus diclofenac. In the perfused hindlimb preparation pretreated with diclofenac, Ach and BK induced a dose-dependent vasodilator response in both wild-type and eNOS(-/-) mice. This response was well preserved after perfusion with L-NAME (300 μM, 30 min) in both mice. The diclofenac- and L-NAME-resistant vasodilator response was blocked by high K^+ concentration, inhibited by K^+ channel blockers (a combination of charybdotoxin and apamin) and gap junction inhibitors, attenuated by soluble guanylyl cyclase inhibitor and CB receptor agonists, but was not affected by the adenosine antagonist, the CYP inhibitors, a combination of phospholipase A_2 and D inhibitors, catalase and hemeoxygenase inhibitor.

Discussion

This study demonstrates that endothelial stimulation releases an EDHF that is a potent endogenous vasodilator of murine resistance vessels both *in vivo* and *in vitro*, and that EDHF is able to completely compensate for the lack of NO in L-NAME-treated wild-type or eNOS(-/-) / mice. The authors suggest that functional gap junctions and calcium-dependent K^+ channels, but not CYP enzymes, soluble guanylyl cyclase, or eNOS play important roles in EDHF-mediated dilation in the mouse hindlimb.

Additional information

References

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