Letter to the Editor

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Hydrogen Sulfide as an Endothelium-Derived Hyperpolarizing Factor in Rodent Mesenteric Arteries

To the Editor:

We read with interest the article by Mustafa et al[1] in *Circulation Research* in which the authors suggest that hydrogen sulfide is a major endothelium-derived hyperpolarizing factor (EDHF) that generates endothelial and vascular myocyte hyperpolarization and relaxation by predominantly activating ATP-sensitive potassium channels (K_{ATP}) through cysteine S-sulfhydration. As previously reported by many groups, Mustafa et al[1] confirm that endothelium-dependent cholinergic relaxations in murine mesenteric artery are minimally affected by combined inhibition of nitric oxide synthase and cyclooxygenase (L-NAME plus indomethacin), observations that are consistent with underlying EDHF-dependent mechanisms. However, it is important to stress that these data do not indicate that nitric oxide and prostacyclin pathways are poorly implicated because ACh-induced relaxations involve various overlapping endothelial mechanisms such that when only one or two are inhibited, full ACh-mediated relaxations can still occur.[2]

In some vessels, nitric oxide or prostacyclin can produce vascular smooth muscle relaxation or hyperpolarization by activating K_{ATP} channels.[2] The surprise of the present study, in rat and mouse mesenteric arteries, is that nitric oxide synthase-independent and cyclooxygenase-independent relaxations/hyperpolarizations were prevented by the K_{ATP} channel blocker glibenclamide. This contrasts with numerous observations generated over nearly three decades by various groups. These previously published findings are clear and show that, in these and other arteries, nitric oxide synthase-independent and cyclooxygenase-independent endothelium-dependent relaxations and hyperpolarizations do not involve K_{ATP} channel activation.[3–7]

In a previous article, Yang et al[8] showed that endothelium-dependent cholinergic relaxations were virtually abolished in mesenteric arteries from cystathionine γ-lyase knockout mice. Direct effects of nitric oxide synthase and cyclooxygenase inhibition are not shown in the present article. However, by comparing Figure 2D[8] with Figure 1A of the present article,[1] it appears that the combination of L-NAME plus indomethacin did not produce any further impairment of endothelium-dependent relaxations in the arteries of cystathionine γ-lyase knockout mice. Therefore, cystathionine γ-lyase deletion per se produces marked endothelial dysfunction involving both of the two predominant parallel mechanisms that underlie endothelium-dependent relaxations, ie, the nitric oxide synthase and EDHF pathways.

We therefore suggest that the overall impairment of these two major vasorelaxant pathways can be reasonably explained by the gross increase in plasma levels of homocysteine observed in cystathionine γ-lyase knockout mice. Homocysteine levels are elevated 10-fold in male cystathionine γ-lyase knockout animals and a staggering 60-fold in comparable female mice.[8] Such hyperhomocysteinemia is known to generate oxidative stress-dependent endothelial dysfunction associated not only with decreased nitric oxide availability[9] but also with a reduction in EDHF-mediated responses by inhibiting activation of small and intermediate conductance calcium-activated potassium channels (SK_{Ca} and IK_{Ca}).[10,11] Therefore, whether the observed diminution in the endothelium-dependent effects of ACh (nitric oxide-mediated and EDHF-mediated responses) reported by Mustafa et al[1] is directly associated with the disruption of cystathionine γ-lyase (ie, lack of hydrogen sulfide) or, alternatively, is merely the consequence of the accompanying hyperhomocysteinemia requires rigorous assessment.

In their article, Mustafa et al[1] have demonstrated the molecular processes that generate hydrogen sulfide-dependent activation of K_{ATP} channels. However, activation of K_{ATP} as the mechanism that underlies the EDHF response has been refuted by virtually the entire community of scientists involved in EDHF research. We feel that the authors must be more cautious in their conclusion that "hydrogen sulfide is a major EDHF in resistance blood vessels."

Disclosures

None.

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