Role of tetrahydrobiopterin (BH4) in hyperhomocysteinemia-induced endothelial dysfunction: new indication for this orphan-drug?

Rinrada Kietadisorn, Bas L. Kietselaer, Harald H. H. W. Schmidt, and An L. Moens

Departments of Cardiology and Pharmacology, Cardiovascular Research Institute, Maastricht University Medical Centre, Maastricht, The Netherlands

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TO THE EDITOR: He et al. (3) presented in the American Journal of Physiology - Endocrinology and Metabolism that chronic hyperhomocysteinemia (HHcy; plasma level of homocysteine >15 μmol/l) impairs coronary artery endothelial function and that plasma levels of nitric oxide (NO) and tetrahydrobiopterin (BH4) are positively correlated and significantly decreased in patients with HHcy compared with controls (99.54 ± 32.23 vs. 119.50 ± 37.68 μmol/l and 1.43 ± 0.46 vs. 1.73 ± 0.56 pmol/ml, all P < 0.05). Moreover, coronary flow velocity reserve (CFVR) was significantly lower (~10%) in the HHcy patients than in the control group. In addition, plasma level of homocysteine was negatively correlated with CFVR and plasma level of NO. He et al. suggested that chronic HHcy decreased plasma NO and BH4, leading to endothelial nitric oxide synthase (eNOS) uncoupling and, consequently, coronary artery endothelium dysfunction.

While the results of He et al. are intriguing, the methodologies used are controversial, and subsequent conclusions are too preliminary. First, the authors used a nitrite/nitrate assay based on the Griess reagent to determine plasma NO levels. Nitrite and nitrate are the degradation products of NO. Unfortunately, this methodology carries some disadvantages when used in serum, as it does not allow an exact differentiation of nitrite and biogenic amines that are physiologically present in plasma and is, hence, not a fully reliable marker to indicate decreases in NO levels or, for that matter, uncoupling of eNOS.

Second, the ratio of BH4 and its oxidized form dihydrobiopterin (BH2) should have been measured instead of plasma BH4 levels alone. A decrease in plasma BH4 levels alone is insufficient to induce and indicate eNOS uncoupling. Indeed, the ratio of reduced and oxidized biopterins (i.e., the BH4/BH2 ratio), and not only the absolute amount of BH4, plays an important role in eNOS coupling in vivo (2). Although BH2 does not have an NOS cofactor property, it inhibits BH4 competitively (5) and binds eNOS with an affinity equal to that of BH4 (1); therefore, BH2 should have been measured.

Third, although transthoracic Doppler echocardiography using adenosine-induced hyperemia is a well-studied method to evaluate coronary flow reserve (CFR), there are several factors influencing CFR. Normal CFR indicates a normal two-compartment system: a patent epicardial vessel supplying a normal myocardial bed. Abnormal CFR may be due to multiple factors such as abnormal epicardial vessels (i.e., flow limiting stenosis), abnormal microvasculature, and factors influencing blood composition and endothelial dysfunction. In addition, there is a large body of evidence showing great variations in CFR due to different medical conditions such as heart failure, hypertension, or even dietary intake (4). In the study of He et al., there is no evidence of absence of flow-limiting coronary artery disease, left ventricular hypertrophy, heart failure, or other factors influencing CFR. As these factors all influence CFR, CFR should not be used as a direct measure of endothelial function in these subjects.

He et al. have paved the way for further research regarding the pathogenetic role of eNOS uncoupling in patients with HHcy, which eventually can lead to the therapeutic use of eNOS modulators (such as BH4) to treat eNOS uncoupling-induced endothelial dysfunction in these patients.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES