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Letter to the editor: Is homocysteine the culprit molecule in vascular diseases or just a bystander?

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TO THE EDITOR: Jiang et al. (3) reported an important finding that vascular smooth cell migration was promoted by the resistin gene expression induced by ultrahigh concentrations of homocysteine (500 μM). The homocysteine concentrations used by Jiang et al. were markedly higher than the physiological concentrations (<100 μM); therefore, the biological significance of the results of their study should be interpreted with caution. Since supraphysiological concentrations of homocysteine are required to induce resistin expression, the role of homocysteine in vascular cell migration is debatable. To assess the effects of homocysteine at physiological levels, Wang et al. (5) developed a method in which erythro-9 (2-hydroxy-3-nonyl)-adenine hydrochloride (EHNA) and adenosine were added to homocysteine to convert homocysteine into its more toxic form *S*-adenosylhomocysteine (SAH). This protocol has been used in many studies to study the effects of homocysteine on gene expression.

The effect of homocysteine on the downregulation of fibroblast growth factor 2 (FGF2) in human coronary artery endothelial cells (HCAECs) is mediated through SAH and not by homocysteine itself (2). We have previously reported that a supraphysiological concentration (500 μM) of homocyteine did not affect the cell integrity of HCAECs. However, when EHNA was added to the cell culture to facilitate the formation of intracellular SAH, homocysteine induced cytotoxic changes at concentrations as low as 25 μM, which is a clinically relevant concentration. Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) revealed that cells exposed to homocysteine and adenosine/EHNA showed at least a two- to fourfold increase in intracellular SAH concentration. In conclusion, we hypothesize that in the absence of SAH, the vascular effects of homocysteine will be negligible even at supraphysiological concentrations of homocysteine.

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The indispensable role of SAH, and not homocysteine, in inducing vascular endothelial damage explains the lack of health benefits in several nutritional intervention trials, despite the increase in vitamin supplements to successfully lower plasma homocysteine levels (1). Since growing evidence suggests that SAH is a better indicator of cardiovascular disease than homocysteine (4), Jiang et al. may want to delineate the relative importance of SAH in resistin regulation in comparison with that of homocysteine in their future studies.

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DISCLOSURES

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