Effect of High Glucose on Vasculature

To the Editor:

Cosentino et al. report that high glucose causes PKC-dependent upregulation of inducible cyclooxygenase and endothelial NO synthase (eNOS) expression in human aortic endothelial cells associated with a selective increase of thromboxane production and reduced NO release. As stated by the authors, these data are in contrast with recent observations that eNOS activity was reduced to 43% in hyperglycemic and/or diabetic aortic cell culture compared with controls. High production of NO resulting from increased inducible NO synthase (iNOS) expression may be linked to increased cardiovascular disease in nondiabetic patients. Recently, we reported that high glucose increased iNOS expression and NO release in working rat hearts. Upregulation of iNOS and raised NO generation were accompanied by a marked concomitant increase of superoxide production. The interaction of superoxide with NO is very rapid and leads to inactivation of NO and production of the potent oxidant peroxynitrite. As nitrotyrosine is considered a good marker of peroxynitrite formation, detection of nitrotyrosine in hearts perfused with high glucose is strongly suggestive for increased generation of peroxynitrite, which can mediate the toxic effects of high glucose on the heart, as suggested by the detection of cell apoptosis. On the other hand, we failed to observe modification of the intensity of eNOS expression in the presence of high glucose. Further studies are needed to evaluate whether upregulation of iNOS by high glucose plays a role in the mediation of its toxic effect on the vasculature.

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Response

We thank Dr. Marfella et al for their letter related to our recent work. As we reported, in spite of a paradoxical upregulation of endothelial NO synthase (eNOS), NO release was reduced, and coinubcation with antioxidants restored the balance between NO and reactive oxygen species formation. These findings are in agreement with the results of a study performed in an in vivo model of diabetes. Although in our study we did not investigate the effect of high glucose on NO synthase activity, we are aware that an impairment of eNOS activity under hyperglycemic conditions could also contribute to reduce NO levels. However, we can rule out that decreases in eNOS gene expression contribute to endothelial dysfunction. At both the RNA and the protein levels, the enzyme is upregulated 2- to 3-fold in human aortic endothelial cells (HAECs) exposed to high glucose and in vessels from diabetic animals.

On the basis of these observations, it is reasonable to hypothesize that the superoxide formed may either overwhelm the NO production of the upregulated eNOS or that the eNOS itself may be uncoupled, thereby contributing to superoxide production. Because there is no evidence of expression of inducible NO synthase (iNOS) messenger RNA in HAECs under normal and inflammatory conditions, the upregulation of iNOS by high glucose observed in working rat heart may not be easily transferred to our experimental setting. However, it is very likely that in the vasculature, the uncoupling of eNOS is associated with induction of iNOS and concomitant increments in NO and superoxide, which may contribute to the formation of high concentration of peroxynitrite in diabetes mellitus.

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