Glomerular endothelial NOS (eNOS) expression in type 2 diabetic patients with nephropathy

Sir,

Bioavailability of nitric oxide (NO) in the diabetic kidney has been a subject of numerous studies in various experimental settings. Paradoxically, both enhanced NO production and endothelial dysfunction, as a consequence of impaired NO generation by endothelial NO synthase (eNOS), have been implicated in the pathophysiology of diabetic nephropathy [1].

In the recent issue of NDT, Hohenstein and co-workers [2] report increases in expression and different patterns of distribution of eNOS in glomeruli from type 2 diabetic patients with nephropathy. The eNOS expression was higher in patients with more severe proteinuria and correlated with the severity of vascular complications. The authors assume that enhanced eNOS protein expression indicates parallel increases in NO production, and state that their findings strengthen the view that NO activity is stimulated in diabetic nephropathy. Moreover, they suggest that the kidney circulation is endowed by a specific ability to upregulate eNOS in the face of decreasing NO bioavailability in the systemic circulation.

The authors should be commended for addressing this issue in the clinical context. However, the data should be interpreted with caution, reflecting current knowledge about eNOS pathobiochemistry in diabetes. To function as an NO-producing enzyme, eNOS requires a battery of cofactors, posttranslational modifications such as phosphorylation and dimerization, protein–protein interactions and subcellular targeting [3]. We have recently explored renal cortical protein expression of eNOS with respect to these determinants of its enzymatic function, in streptozotocin-diabetic (DM) rats and control animals [4]. Despite similar whole cell eNOS expression in all groups, eNOS monomer and dimer in membrane fractions were reduced in DM compared to controls; the opposite trend was apparent in the cytosol. Stimulatory phosphorylation of eNOS on Serine 1177 was also reduced in DM. Some of these findings are consistent with eNOS ‘uncoupling’ in the diabetic kidney, i.e. a phenomenon characterized by diversion of electron transfer within the eNOS molecule from L-arginine oxidation, resulting in reduction of molecular oxygen to form superoxide instead of NO. Indeed, parallel studies by others [5] proved eNOS uncoupling as the major source of local superoxide production in the diabetic kidney. Together, these studies indicate that mere determination of total eNOS protein, without consideration of posttranslational modifications, does not provide sufficient information with respect to eNOS-mediated NO generation. Increases in eNOS in diabetic glomeruli observed by Hohenstein et al. are likely to reflect the pool of the enzyme that is not active in eNOS generation, but contributes to superoxide production. Clearly, a clinical study utilizing kidney biopsies cannot provide data reflecting the above-mentioned characteristics of eNOS. However, some determinants, in particular eNOS phosphorylation status, could be determined even in human biopsy material. We look forward to further clinical studies in this very important disease.

Conflict of interest statement. None declared.

Radko Komers
Division of Nephrology and Hypertension, Oregon Health and Science University, Portland, OR, USA
E-mail: rako@medicon.cz, komersr@ohsu.edu


do: 10.1093/ndt/gfn174

Advance Access publication 10 April 2008

Reply

Sir,

In response to the comment by Komers and Anderson we would like to add some important thoughts to the discussion on the relevance of the present study [1]. Several studies demonstrating the relevance of many cofactors and modifications of the eNOS enzyme have been published but a discrepancy between patient related and experimental data may occur [2]. Clearly, one major concern with respect to the arguments forwarded by Komers and Anderson is the comparability of experimental models and human...