Response to Comment on: Ott et al. Reduction in Basal Nitric Oxide Activity Causes Albuminuria. Diabetes 2011;60:572–576

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We thank Tsikas et al. (1) for their interest in our recent work. Tsikas et al. comment that we did not provide direct evidence of reduced nitric oxide (NO) synthesis. No direct approach is available in humans. However, N^G-monomethyl-L-arginine (L-NMMA) is a specific NO synthase (NOS) inhibitor, i.e., the changes we reported are due to NOS inhibition. In the cited publication by Tsikas et al., long-term (chronic) effects and indirect markers of (systemic) NO metabolism (plasma nitrites and nitrates) but not endothelial NOS (eNOS) activity were measured (2). Administration of L-NMMA was associated with altered renal hemodynamics and decreased plasma and urinary excretion of nitrites and nitrates (3). Others have shown reduced cGMP levels with N^G-nitro-L-arginine methyl ester (L-NAME) (4). Of note, we believe that the rise of blood pressure is a poor marker of the degree of NOS blockade, since an intact baroreflex counteracts the rise of blood pressure. The vascular effects of L-NMMA (vasoconstriction) are therefore underestimated when simply looking at the blood pressure increase (5).

In animal studies, the specificity of L-NMMA can be more accurately assessed. Inhibition of NOS activity with L-NMMA lead in a dose-dependent manner to an increased glomerular capillary permeability of albumin (6), and an eNOS knock-out model developed significantly increased albuminuria (7). These experiments substantiate the claim that L-NMMA profoundly inhibits eNOS and as consequence causes albuminuria.

Tsikas et al. suggest that other mediators, in particular thromboxane, may be involved. Because of the strong evidence (3,4,7) we are convinced that the changes observed are predominantly or even exclusively caused by specific NOS inhibition, but we cannot rule out that other factors might have contributed to albuminuria. In principle, thromboxane could be one of these mediators, but several previous studies suggest that this may not be the case. In the cited publication of Francois et al. (8), chronic L-NAME administration elevates concentrations of thromboxane B_2 (TxB_2) and 8-isoprostanes. However, urinary albumin excretion did not change over time. In streptozotocin-induced diabetic rats the thromboxane synthetase inhibition resulted in a significant reduced urinary TxB_2 excretion, whereas urinary protein excretion did not differ significantly (9).

Thus our study demonstrates that reduced NO activity causes an increase in albuminuria in humans.

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