

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

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Ott et al. (1) reported that systemic nitric oxide (NO) synthase (NOS) inhibition with N^G -monomethyl-L-arginine (L-NMMA) (2) acutely increased the urinary albumin-to-creatinine ratio in hypertensive patients with type 2 diabetes. The authors did not provide direct evidence of reduced NO synthesis by L-NMMA. The pressor response to the NOS inhibitors L-NMMA, asymmetric dimethylarginine (ADMA), and N^G -nitro-L-arginine methyl ester (L-NAME) is relatively small, given their low inhibitory potency toward endothelial NOS (eNOS) activity (2). Release of thromboxane A_2 (Tx A_2), a potent vasoconstrictor and thromboxane-prostanoid (PT) receptor agonist, and the F_2 -isoprostane 15(*S*)-8-*iso*-prostaglandin $F_{2\alpha}$ (15(*S*)-8-*iso*-PGF $_{2\alpha}$), a vasoconstrictor and functional PT receptor agonist, could also be involved. In mice (3), L-NAME induced hypertension, caused cardiac hypertrophy, and elevated Tx A_2 and 15(*S*)-8-*iso*-PGF $_{2\alpha}$ synthesis. In hypertensive type 2 diabetic subjects, the angiotensin 2 receptor inhibitor olmesartan reduced blood pressure and 15(*S*)-8-*iso*-PGF $_{2\alpha}$ synthesis without changing eNOS activity and ADMA synthesis (4). We propose that in the study by Ott et al. (1), excessive renal Tx A_2 and 15(*S*)-8-*iso*-PGF $_{2\alpha}$ synthesis and PT receptor activation may have contributed to albuminuria (5,6).

Systemic infusion of unspecific eNOS inhibitors such as L-NMMA, L-NAME, or ADMA is not a specific procedure to determine local effects of eNOS inhibition in the kidney.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

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DOI: 10.2337/db11-0519

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