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

Dimitrios Tsikas, Stefan Engeli, Jens Tank, Dirk O. Stichtenoth, and Jens Jordan

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 (TxA_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 TxA_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 TxA_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.

REFERENCES

1. Ott C, Schneider MP, Delles C, Schlaich MP, Schmieder RE. Reduction in basal nitric oxide activity causes albuminuria. Diabetes 2011;60:572–576
2. Tsikas D, Böger RH, Sandmann J, Bode-Böger SM, Frölich JC. Endogenous nitric oxide synthase inhibitors are responsible for the L-arginine paradox. FEBS Lett 2000;478:1–3
3. Francois H, Makhanova N, Ruiz P, et al. A role for the thromboxane receptor in L-NAME hypertension. Am J Physiol Renal Physiol 2008;295: F1096–F1102
4. Fliser D, Wagner KK, Loos A, Tsikas D, Haller H. Chronic angiotensin II receptor blockade reduces (intra)renal vascular resistance in patients with type 2 diabetes. J Am Soc Nephrol 2005;16:1135–1140
5. Tajiri Y, Inoguchi T, Umeda F, Nawata H. Reduction of urinary albumin excretion by thromboxane synthetase inhibitor, OKY-046, through modulating renal prostaglandins in patients with diabetic nephropathy. Diabetes Res Clin Pract 1990;10:231–239
6. Esmatjes E, Conget JI, Gaya J, et al. Effects of thromboxane synthesis inhibitor triflusal on renal hemodynamics in microalbuminuric diabetic patients. Diabetes Care 1990;13:1114–1117

From the Institute of Clinical Pharmacology, Hannover Medical School, Hannover, Germany.
Corresponding author: Dimitrios Tsikas, tsikas.dimitros@mh-hannover.de.
DOI: 10.2337/db11-0519
© 2011 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details.