HO-1 Attenuates Hypertension-Induced Inflammation/ Oxidative Stress: Support From Bartter’s/ Gitelman’s Patients

Lorenzo A. Calò1, Maria Fusaro2 and Paul A. Davis3

To the Editor: Yu and coworkers, in their article titled “Celastrol Attenuates Hypertension-Induced Inflammation and Oxidative Stress in Vascular Smooth Muscle Cells via Induction of Heme Oxygenase-1,” have recently demonstrated in an animal model that the anti-inflammatory and antioxidant celastrol attenuates hypertension-induced inflammation and oxidative stress via induction of heme oxygenase-1 (HO-1), a key protein involved in oxidative stress-related defense, including anti-inflammation. These positive effects were reported at molecular level (in terms of reduced gene and protein expression of inflammatory cytokines), at metabolic level (in terms of reduced insulin resistance), and at histological and molecular level (in terms of reduced cardiovascular remodeling), which were abolished by HO-1 inhibition. The authors propose HO-1 induction as the underlying molecular mechanism. This proposed role of HO-1 is in keeping with the effects of HO-1 induction on the reduction of blood pressure and the interruption/counteraction of the renin–angiotensin–aldosterone system including inflammation and oxidative stress previously demonstrated in an animal model of renovascular hypertension.2

We would like to suggest that the results of our ongoing studies in patients with Bartter’s/Gitelman’s syndromes (BS/GS), a human model characterized by activation of antiatherosclerotic and anti remodeling defenses,3,4 may provide further support for the contention of Yu et al. regarding the effects of inducing HO-1 for the treatment of hypertensive long-term complications as well as additional evidence for the anti-remodeling properties of HO-1 induction in humans. Of direct relevance to the report of Yu et al. in animals is our demonstration that HO-1 is overexpressed in BS/GS patients.5 They also have reduced oxidative stress as shown by reduced expression of oxidative stress-related proteins such as p22phox, a NADPH oxidase subunit, and PAI-1 (ref. 5) in addition to reduced susceptibility of low-density lipoprotein to oxidation.

BS/GS, caused by gene defects in specific kidney transporters and ion channels, presents a puzzling clinical picture characterized by the activation of the renin–angiotensin–aldosterone system, with increased plasma levels of angiotensin II (Ang II) and aldosterone, yet normotension/hypotension reduced peripheral resistance and hyporesponsiveness to pressor agents.3,4 Therefore, understanding why patients with BS/GS do not develop hypertension and its long-term complications (cardiovascular remodeling and atherogenesis), in spite of high Ang II, may shed considerable light on the cellular basis of hypertension. In BS/GS patients, the short-term Ang II signaling leading to vasoconstriction is blunted4 and, as we have reported, levels of CRP, acute phase reactants, and inflammatory process-related cytokines were unchanged compared to normotensive healthy subjects, despite high Ang II levels. In addition, we have shown in BS/GS patients, IkB, the inhibitory subunit of NF-κB, is increased indicating a reduced activity of NF-κB and NF-κB-mediated transcription of genes involved in inflammation and remodeling (including, in particular, ERK1/2) is reduced. Thus in BS/GS, the absence of endothelial dysfunction, the reduced activity of RhoA/Rho kinase system,3,6 the activation of nitric oxide system,3,4 the increased insulin sensitivity, and the lack of cardiovascular remodeling in terms of left ventricular hypertrophy and carotid intima–media thickness (which we documented in BS/GS patients, in addition to their reduced oxidative state3 and HO-1 overexpression5) depict a picture which is the opposite of hypertension. All these biochemical and molecular characteristics of BS/GS (including, in particular, HO-1 overexpression) strongly support, with data from a human model characterized by activation of antiatherosclerotic and anti remodeling defenses, the evidence and conclusions of Yu et al. provided in animals via induction of HO-1 with celastrol.1

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1Department of Clinical and Experimental Medicine, Clinica Medica 4, University of Padova, Padova, Italy; 2Department of Medical and Surgical Sciences, Nephrology, University of Padova, Padova, Italy; 3Department of Nutrition, University of California, Davis, California, USA. Correspondence: Lorenzo A. Calò (renzcalo@unipd.it) doi:10.1038/ajh.2010.130 © 2010 American Journal of Hypertension, Ltd.