Tetrahydrobiopterin and hypertension: more than an emigrating story

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IN THIS ISSUE OF the American Journal of Physiology-Heart and Circulatory Physiology, Kang et al. (2) demonstrated that antihypertensive treatments, e.g., triple therapy with reserpine + hydrochlorothiazide + hydralazine or oral tetrahydrobiopterin (BH4), increase vascular BH4 levels and the ratio of BH4 to 7,8-dihydrobiopterin (BH2), restore nitric oxide (NO)/cGMP signaling, and restore endothelial NO synthase (NOS3) phosphorylation at Ser1177 in small mesenteric arteries from angiotensin II-infused rats. Decreased levels of BH4 have been demonstrated both in the vasculature (1) and the myocardium (3), respectively, by using a model of salt-sensitive low renin-induced hypertension and aortic banding-induced hypertension. So far, the data showing that antihypertensive treatment itself can restore BH4 and NO levels were missing.

The data of Kang et al. (2) are both challenging and intriguing because they further unravel the antihypertensive effects of these drugs and demonstrate that these antihypertensive therapies lower blood pressure through a BH4-dependent mechanism, restoring NO/cGMP signaling and NOS3 phosphorylation in small arteries. However, no data are provided regarding the effects of these therapies on the BH4 levels and the NOS3-uncoupling status in large arteries or in the myocardium. Further mechanistic insight is needed to improve this somewhat premature finding and to investigate whether these data can be extrapolated to ventricular remodeling, an important consequence of hypertension, associated with decreased BH4 levels in the myocardium (3).

In addition, the combination of reserpine, hydrochlorothiazide, and hydralazine is not reflective of the current standards of care with respect to the treatment of hypertension in patients. How much of the decrease in hypertension is due to each drug is one major question that needs answering. In addition, the mechanism of hydralazine is not completely clear, and there is evidence that it directly increases cGMP activity (4).

Furthermore, Kang et al. (2) demonstrate that triple therapy (but not oral BH4 therapy) significantly increases guanosine triphosphate cyclohydrolase (GTPCH)-I activity in small arteries without a change in GTPCH-I expression. Although it is known that shear stress can affect GTPCH-I expression and activity (5), previous studies have not examined this correlation in models of systemic hypertension. Therefore, this study further explores the pathogenesis of hypertension and provides new therapeutic strategies to tackle hypertension.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES