Inducible Nitric Oxide Synthase Inhibition as a Target for the Treatment of Vascular Dysfunction in Hypertension

To the Editor:

Since its discovery, NO has been recognized as a protective molecule for vascular function via its vasodilatory, antithrombotic, and antiapoptotic effects. The role of NO synthase (NOS) in the physiological control of vascular tone was clarified by experiments with the systemic administration of the pharmacological competitor NOS inhibitor, N^\text{G}^-\text{nitro-L-arginine}, which increases blood pressure in experimental animals. The spontaneous development of hypertension in mice with the endothelial isoform of NOS deleted demonstrated that endothelial cell-derived NO promotes vasodilation and opposes the development of hypertension.

On the other hand, Smith et al\(^1\) demonstrated an upregulation of inducible NOS (iNOS) in microvessels of hypertensive subjects and an impressive restoration of the endothelial-dependent vasodilation in hypertensive patients in the presence of a selective iNOS inhibitor. The authors also showed that the increased iNOS levels are associated with decreased phosphorylation of vasodilator-stimulated phosphoprotein in microvessels from hypertensive individuals compared with their matched controls.\(^1\)

To think of iNOS-derived NO as a contributor to the vasodilatory-stimulated phosphoprotein in microvessels from spontaneously hypertensive rats may initially seem a paradox. However, the authors hypothesized that iNOS-mediated increased arginase activity consumes the NO precursor arginine, causing endothelial isofrom of NOS uncoupling and microvascular dysfunction.\(^1\)

Many proteins can be posttranslationally modified by NO-derived species, such as peroxynitrite. In fact, NO can rapidly convert to peroxynitrite in the pro-oxidant environment found in vessels under high blood pressure levels. Peroxynitrite, in turn, reacts with tyrosine residues in proteins modifying them to nitrotyrosine. As already demonstrated, iNOS inhibitors ameliorate the endothelium-dependent dilation in aortas from spontaneously hypertensive rats\(^2\) and from aged rats.\(^3\) This effect was accompanied by a decrease in vascular nitrotyrosine levels, making iNOS inhibition an interesting target for the treatment of vascular dysfunction.\(^2,3\)

However, available data on the safety of drugs that inhibit iNOS enzyme activity are still very preliminary. A therapeutic alternative to iNOS inhibition is to explore the differential mechanisms involved in the regulation of the enzymatic activity of endothelial isoform of NOS and iNOS. Although endothelial isoform of NOS activity is regulated by many posttranscriptional modifications, iNOS is essentially regulated at the transcriptional level. One important regulator of iNOS expression is the nuclear factor-κB. Along with the first report suggesting iNOS as a hypertensive factor, it was also demonstrated that inhibition of either iNOS or nuclear factor-κB activation results in decreased levels of nitrotyrosine and improvement of endothelium-dependent vasorelaxation.\(^2\) Pyrrolidine dithiocarbamate has been used in experimental models of hypertension, resulting in decreased vascular iNOS upregulation and an associated amelioration of NO-dependent vasorelaxation and vascular remodeling.\(^4\) Thus, the association of pyrrolidine dithiocarbamate to antihypertensive therapy should be considered, because it represents a preventive way to inhibit iNOS expression and the vascular dysfunction associated with its activity. Although pyrrolidine dithiocarbamate was shown to be safe in different doses and routes of administration in preclinical studies,\(^5\) additional data on its safety in humans as well as on the mechanisms involved in its beneficial vascular effects are warranted.

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