Lysyl Oxidase Inhibition Is Responsible for the Vascular Elastic Fiber Phenotype

To the Editor:

In the July issue of Hypertension, Mercier et al demonstrated a rat model in which the structural vascular phenotype is modified in response to amine oxidase inhibition by semicarbazide. Under these conditions, the elastic lamellae presented globular masses along their periphery, and focal disorganization was observed in the ascending aorta. Immunofluorescence microscopy demonstrated branching of elastic lamellae and a sparse hairy aspect of some elastic fibers after amine oxidase inhibition. Because the above-described abnormalities are not found in semicarbazide-sensitive amine oxidase–deficient mice, the authors conclude that these effects cannot be attributable to amine oxidase inhibition. However, semicarbazide-mediated inhibition of amino oxidase was associated with decreased lysyl oxidase (LOX) activity. From their data, the authors assume that this LOX inhibition might be responsible for the major part of the vascular phenotype of semicarbazide-treated rats.

Our studies on the regulation of vessel wall integrity and plaque stability by mediators of inflammation, ie, the proinflammatory cytokine granulocyte macrophage colony–stimulating factor (GM-CSF), strongly support the hypothesis of Mercier et al that the observed elastic phenotype is related to LOX inhibition. As recently shown by our group, GM-CSF(−/−) mice show abnormalities of the elastic system with striking similarity to those described in the present article for rats after semicarbazide treatment, ie, amorphous matrix lining the surface of the elastic lamellae, elastic fiber hypertrophy as we classified it or as stated by Mercier et al, a hairy aspect of some elastic fibers. Moreover, ultrastructural analysis revealed that GM-CSF(−/−) mice show also collagen fiber abnormalities: disorganized collagen bundles and abnormal collagen fibers with widely varying diameters. Taken together, our data pointed to compromised fiber cross-linkage. Indeed, expression of LOX and of the LOX-activator bone morphogenic protein was reduced in the aorta of GM-CSF(−/−) mice. Moreover, treatment of vascular smooth muscle cells with GM-CSF stimulated the expression of LOX.

Thus, the observed changes in the elastic fiber system of the aorta of semicarbazide-treated rats are highly compatible with the elastin phenotype of GM-CSF(−/−) mice. Furthermore, the elastic phenotypes of both models are in line with the phenotype of LOX-deficient mice, suggesting that the molecular mechanism underlying the formation of abnormal elastic lamellae in both animal models is the compromised elastic fiber cross-linkage as a result of reduced LOX activity or expression.

Because both semicarbazide-sensitive amine oxidase andflammatory mediators are increased in processes of vascular inflammation and because semicarbazide-sensitive amine oxidase inhibition is associated with a downregulation of inflammatory mediators, the relation between ECM-modulating inflammatory mediators, such as GM-CSF and semicarbazide-sensitive amine oxidase, should be addressed.

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