Letter to the editor: “Looking for molecular mechanisms underlying aberrant elastin deposition in hypertension”

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TO THE EDITOR: Elastic fibers may be key elements in the pathophysiology of hypertensive vascular remodeling. In addition to the well-known adverse effects of hypertension on the elastic fiber system, recent studies indicate that aberrant elastin deposition may precede the development of hypertension.

In the December 2008 issue of American Journal of Physiology-Heart and Circulatory Physiology, Arribas and coworkers (1) demonstrated the deposition of excessive and aberrant elastin before the development of systemic hypertension in spontaneously hypertensive rats (SHRs). In neonatal SHRs, the isolated elastin scaffold of the aorta exhibited an increased relative weight and stiffness, as well as the presence of peculiar trabeculae inside the fenestrae that reduced their size. The authors concluded from their data that the aberrant elastin deposited in the SHR aorta alters the mechanical properties leading to compromised vessel expansion, compromised hemodynamic function, and finally to the development of hypertension. Since the abnormal organization does not occur in nongenetic models of hypertension, the authors speculate that a unique genetic program of SHRs triggers an early aberrant assembly of elastic lamellae and/or a lack of normal elastin remodeling.

However, the underlying genetic components are still unknown. Evidence is steadily mounting that inflammatory mediators are important players in the pathophysiology of human essential hypertension. Serum levels of inflammatory markers, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and monocyte chemoattractant protein-1 (MCP-1), are elevated in patients with arterial hypertension (3). Interestingly, in clinical trials, the mild side effects of recombinant human GM-CSF treatment included hypertension (4). Reportedly, GM-CSF is a stimulator of MCP-1 (5).

SHRs exhibit inflammation and cerebrovascular hypertrophy. Recent studies related neurogenic hypertension to vascular inflammation of the brain stem (4). Conversely, statins exerted their antiinflammatory effect via anti-inflammatory pathways, i.e., by downregulating the expression of MCP-1 (6). However, the underlying genetic components are still unknown. Evidence is steadily mounting that inflammatory mediators are important players in the pathophysiology of human essential hypertension. Serum levels of inflammatory markers, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and monocyte chemoattractant protein-1 (MCP-1), are elevated in patients with arterial hypertension (3). Interestingly, in clinical trials, the mild side effects of recombinant human GM-CSF treatment included hypertension (4). Reportedly, GM-CSF is a stimulator of MCP-1 (5).

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Our studies on the regulation of vessel wall structural integrity by mediators of inflammation (5) demonstrated that GM-CSF is also a regulator of elastin production and assembly. Furthermore, our studies on GM-CSF-deficient mice pointed to compromised elastic fiber cross-linkage as a result of a decreased expression of lysyl oxidase. In reverse, the treatment of vascular smooth muscle cells with GM-CSF stimulated the expression of lysyl oxidase (9), and in SHR, aortic lysyl oxidase activity is increased (6).

Taken together, these observations are consistent with the notion that the proinflammatory mediator and extracellular matrix regulator GM-CSF participates in the cytokine network triggering the structural abnormalities associated with hypertension. In our opinion, the relationship between GM-CSF and the formation of an aberrant elastin system in the developmental phase and in the established stage of hypertension merits serious consideration.

REFERENCES


