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Beneficial Aspects of Vascular Apoptosis in Hypertensive Heart Disease

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Arterial hypertension may be viewed as a generalized vascular disorder, with an imbalance between proliferation and apoptosis of vascular smooth muscle cells. As a consequence exaggerated accumulation of these cells may result leading to an encroachment of the tunica media into the lumen. This geometric abnormality of the vessel wall may play a critical role in the long-term maintenance of elevated blood pressure and development of hypertensive endorgan damage. In this short paper, we summarize data on alterations in the growth and death of vascular smooth muscle cells in the small coronary arteries in hypertension. *J Clin Basic Cardiol 2000; 3: 61–2.*

Arterial hypertension is often associated with cardiac complications. The major cardiac alteration is left ventricular hypertrophy (LVH), which may be implicated in the development of coronary insufficiency and arrhythmia and may lead to congestive heart failure [1]. In addition, abnormalities that occur in coronary vessels are aggravated by hypertension. In humans, atherosclerosis at the level of epicardial coronary arteries is accelerated by hypertension and is often complicated by partial or complete occlusion of the vessel lumen and/or plaque rupture with or without thrombosis, leading to myocardial infarction. In addition, microvascular disease affecting intramyocardial vasculature typically occurs in the heart in hypertension and may cause angina even in the presence of normal epicardial coronary arteries [2].

The intramyocardial precapillary vascular tree comprises small arteries and arterioles. These vessels present significant alterations in hypertension, as demonstrated in different hypertensive models [3] and hypertensive patients [4]: increased media thickness, decreased lumen, increased media-to-lumen ratio, and sometimes increased media cross section. Exaggerated accumulation of vascular smooth muscle cells (VSMCs) appears to be responsible for encroachment of the tunica media into the lumen that occurs in small arteries in hypertension [5]. In agreement with that we [6, 7] and others [8] have reported recently that small intramyocardial arteries of adult spontaneously hypertensive rats (SHR) with LVH exhibit abnormally high media thickness and VSMC hyperplasia.

Proliferation and death of VSMCs

It has been hypothesized that an imbalance between exaggerated proliferation and depressed apoptosis might be involved in abnormalities of VSMC growth in hypertension [9]. Some recent experimental observations from our group support that notion [7]. In fact, we studied the simultaneous expression of the cytoplasmic proteins Bax and Bcl-2, respectively a promoter and an inhibitor of apoptosis, and the expression of cyclin A, a nuclear protein that induces proliferation, in VSMCs of small intramyocardial arteries from the left ventricle of adult SHR and adult normotensive Wistar-Kyoto rats (WKY). Compared with WKY, cells from SHR exhibited normal Bax expression, increased ($p < 0.001$) Bcl-2 expression, and increased cyclin A ($p < 0.001$) expression. The ratio of Bax to Bcl-2, an index of cell susceptibility to apoptosis, was lower ($p < 0.001$) in SHR than in WKY. Thus, apoptosis and proliferation of VSMCs might be inhibited and stimulated, respectively, in small intramyocardial arteries of adult SHR.

Regulation of the cell growth/cell death balance during antihypertensive therapy, particularly during the process of cardiac hypertrophy regression, is poorly understood. We have reported that chronic administration of the angiotensin converting enzyme inhibitor quinapril to SHR normalizes proliferation of VSMCs in small intramyocardial arteries from the left ventricle, possibly by inhibiting the expression of the oncoprotein c-Myc and its effect on the cell cycle [10]. In an other study we found that Bax and Bcl-2 expression were stimulated and inhibited, respectively, in VSMCs of small intramyocardial arteries from SHR chronically treated with quinapril [11]. As a consequence, the ratio of Bax to Bcl-2 and, thus, the susceptibility to apoptosis was normalized in treated SHR. Similar results have been reported by deBlois et al. [12] showing that the angiotensin II type 1 receptor antagonist losartan stimulates VSMC apoptosis in vivo in SHR.

Conclusions

The imbalance between replication and apoptosis may account for abnormalities of VSMCs involved in alterations of vascular wall structure and geometry present in small coronary vessels in hypertension. The restoration of the normal balance between VSMC growth and death may contribute to the reparation of coronary wall structure in hypertensive heart disease. This, in turn, may have a beneficial impact on perfusion and oxygen supply to the myocardium in hypertensives presenting this cardiac complication. It can, thus, be proposed that the induction of VSMC apoptosis may be a target of antihypertensive treatment in patients with hypertensive cardiomyopathy. Further studies are required to elucidate whether this property is restricted to compounds that interfere with the renin-angiotensin system or is also shared by other antihypertensive drugs.

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