metallothionein Reverses the Harmful Effects of Angiotensin II on the Diabetic Heart*

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It is well known that the high incidence of diabetes represents a serious cause of morbidity and mortality in part as the result of cardiovascular complications such as hypertension, coronary artery disease, and stroke (1). Cardiac remodeling, including fibrosis and left ventricular hypertrophy, is found in the diabetic heart (2) as a result of the activation of the renin angiotensin system. The contributing role of angiotensin (Ang) II to diabetic cardiomyopathy has been recognized, a finding supported by the beneficial role of Ang II AT1 receptor blockers and angiotensin-converting enzyme (ACE) inhibitors, which reduce morphologic abnormalities, including myofibrillar remodeling (3). Indeed, the inhibition of the renin angiotensin system has been shown to prevent the generation of atherosclerosis in animal models (1) and the production of cardiac fibrosis, improving impulse propagation with a consequent decrease in the incidence of re-entrant rhythms (4).

See page 655

Diabetic cardiomyopathy is a clinical condition in which ventricular dysfunction is found in the absence of hypertension and coronary atherosclerosis (5,6). A notable and significant association between diabetes and heart failure in which diastolic dysfunction is the predominant factor has been described (7). Studies performed by Zhou et al. (8) in this issue of the Journal using cardiac-specific metallothionein-overexpressing transgenic mice showed that the harmful effects of Ang II on the diabetic heart, including apoptosis, fibrosis, and nitrosative lesions, are greatly reversed by metallothionein—a cysteine-related protein able to scavenge free radicals, including superoxide and peroxynitrite (9). The authors of several studies associate diabetes with zinc deficiency and discuss the possibility that zinc induces metallothionein synthesis in animals and humans (10). Moreover, the possible relation-ship between zinc deficiency and heart failure has been recently re-evaluated (11), taking into consideration that ACE and matrix metalloproteinases are zinc enzymes that play a role on cardiac remodeling. Moreover, thiazide diuretics, which are frequently used in patients with heart failure and hypertension, cause zincuria and a decrease in tissue levels of zinc (11).

The fundamental mechanism involved in the beneficial effect of metallothionein is the decrease of oxidative stress. It is known that Ang II stimulates superoxide production via the AT1 receptor by activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which is localized in many tissues, including vascular smooth muscle cells, fibroblasts, and heart tissue (12). Indeed, enhanced levels of Ang II found in different pathophysiologic conditions such as hypertension and heart failure cause increased superoxide production concurrently with a decrease in nitric oxide activity (13–15). Angiotensin II induces activation of NADPH oxidase, enhances the expression of NADPH subunits, and stimulates reactive oxygen species production in vascular smooth muscle in vitro as well as in intact arteries (16,17). Although different possible mechanisms are involved in the prevention of Ang II–mediated cardiac damage in diabetes, the work of Zhou et al. (8) presents evidence that metallothionein suppresses NOX p47phox activation as well as oxidative and nitrosative damage. It is known that the beneficial effects of AT1 blockers and ACE inhibitors in diabetic cardiomyopathy are in part related to the increased availability of nitric oxide (18), a view supported by the finding that the use of olmesartan decreased oxidative stress and hypoxia-induced left ventricular remodeling in part through inhibition of nuclear factor-kappa B and matrix metalloproteinase-9 activities (19). In patients with essential hypertension, for instance, the use of valsartan reduced QTc dispersion—an effect probably related to its antioxidative stress effect (20), whereas in age-dependent cardiomyopathy found in ACE-2-null mice, the increased level of Ang II mediated the oxidative stress and the neutrophilic infiltration (21).

Antioxidants have a potential value in the treatment of several cardiovascular diseases involving oxidative stress (22–23). Large clinical trials such as CHAOS (Cambridge Heart Oxidant Study) (24) and ASAP (Anti-oxidant Supplementation in Atherosclerosis Prevention) study (25) showed positive results, whereas other trials were not as convincing (26). Nitrosative and oxidative changes of proteins can modify enzyme functions and protein localization, and different enzymes involved in the generation of reactive oxygen species are located in different subcellular compartments (27) and exert different functions. Because an ideal antioxidant should be able to remove a nitro group from an altered protein without generating any other effect (28), it is difficult to achieve this goal and to analyze its beneficial effect for human beings. This justifies the contin-

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uous effort to increase our knowledge in this important area of cell biology and pathology.

The implications of these findings for cardiology are many. It is known, for instance, that the infarct sizes in patients with diabetes-associated hyperglycemia are much larger than those in nondiabetic patients (29), which indicate that stress hyperglycemia enhances the sensitivity of cardiac muscle to injury. Moreover, an association between oxidative stress and atrial fibrillation has been described (30). The work of Zhou et al. (8) improves our knowledge of how to reduce the cardiac damage elicited by diabetes in animals by reversing the oxidative stress caused by Ang II and opens the possibility of using antioxidants for the prevention of cardiac damage in diabetic patients.

Certainly, additional clinical studies as well as the use of clinical markers and the determination of end points are necessary to translate these pre-clinical studies and provide good management for diabetic patients with a clear risk of cardiomyopathy. For instance, thioredoxin, which is a redox-acting protein and considered to be a biomarker for several cardiovascular diseases associated with oxidative stress, is useful for diabetic patients with risk of cardiomyopathy (31), and the same seems to be true for homocysteine, which is considered an important source of oxidative stress in cardiomyopathy (31). Because there is a synergism between hyperglycemia and inflammation, the use of inflammatory markers such as monocyte chemoattractant protein-1 and the von Willebrand factor is also useful (32). In the case of atrial fibrillation, which has been associated with myocardial oxidative stress, the use of serum markers of oxidation and inflammation can be useful. Indeed, a recent study (30) supports the view that oxidative stress markers such as derivatives of reactive oxidative metabolites and ratios of oxidized to reduced glutathione as well as cysteine are useful in patients with persistent atrial fibrillation. Although there is evidence that dietary supplementation with vitamin E improves heart failure in human type 1 diabetic cardiomyopathy through the suppression of oxidized glutathione and 8-iso prostaglandin F2-alpha (33), the causes of diabetic cardiomyopathy remain elusive (34). Indeed, epidemiological studies have indicated structural abnormalities in the left ventricle before the evidence of clinical diabetes (34). Further translational studies on metabolic, functional, and structural changes in the diabetic heart will help to clarify the etiology of diabetic cardiomyopathy.

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