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COMMENTARY

Diabetic cardiomyopathy: how much does it depend on AGE?

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Diabetic cardiomyopathy refers to dysfunction of cardiac muscle in patients with diabetes that cannot be directly ascribed to hypertension, coronary heart disease or other defined cardiac abnormalities *per se*. The development of diabetic cardiomyopathy may involve several distinct mechanisms, including increased formation of advanced glycation end products (AGEs) secondary to hyperglycaemia. AGEs may alter structural proteins and lead to increased arterial and myocardial stiffness. Therefore, therapies that prevent or retard development of AGEs in diabetes may be valuable strategies to treat or prevent diabetic cardiomyopathy. In this issue of *British Journal of Pharmacology*, Wu and colleagues demonstrate that aminoguanidine (inhibitor of AGE formation and protein cross-linking) treatment of a rat model of type I diabetes (rats made insulin deficient with streptozotocin and nicotinamide treatment) ameliorates detrimental changes in left ventricular structure and function. Results from this study are in agreement with previous investigations, suggesting that aminoguanidine is effective in preventing cardiac hypertrophy and arterial stiffening in experimental animal models of diabetes and emphasize the potential pathogenic role of AGEs in diabetic cardiomyopathy.
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Abbreviation: AGE, advanced glycation end products

Cardiovascular complications are the leading cause of diabetes-related morbidity and mortality (Goede *et al*., 2008). Increased risk of heart failure in patients with diabetes is largely related to accelerated atherosclerosis and hypertension. However, compelling epidemiological and clinical data strongly suggest that diabetes *per se* confers additional risk for cardiac dysfunction and heart failure, independent of coronary artery disease and hypertension. Thus, diabetic cardiomyopathy (Rubler *et al*., 1972) has been the subject of intensive investigation over the last 30 years. Nonetheless, the pathogenesis of diabetic cardiomyopathy is still far from being fully elucidated. Functional and structural changes in diabetic heart may result from metabolic disturbances, abnormalities in ion homeostasis, cardiac autonomic neuropathy and/or alterations in structural proteins (Fang *et al*., 2004). Thus, increased formation of advanced glycation end products (AGEs) secondary to persistent hyperglycaemia has emerged as an important contributor to the development of diabetic cardiomyopathy (Avendano *et al*., 1999).

AGEs arise from intracellular autooxidation of glucose to glyoxal, decomposition of the Amadori product, and fragmentation of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate to methylglyoxal. These reactive intracellular dicarbonyls interact with amino residues of proteins, including elastin and collagen, to alter the functional properties of matrix components that mediate sustained cellular changes (Brownlee *et al*., 1988). Accumulating evidence suggests that cross-bridge formation between AGEs and structural proteins including collagen leads to increased arterial and myocardial stiffness during ageing, hypertension and diabetes. As a consequence, strategies that prevent AGE formation, block activation of AGE receptors or break the AGE–protein cross-links have been suggested as potential therapies to attenuate pathogenic influences of AGEs on myocardial function in diabetes.

One of the most extensively used inhibitors of AGE formation, aminoguanidine, is a small nucleophilic compound that prevents cross-link formation by interacting with post-Amadori reactive intermediates to avert AGE creation from di-carbonyl precursors. Following the demonstration that aminoguanidine attenuates formation of diabetes-induced AGEs and cross-linking of connective tissue proteins in the arterial wall *in vivo* (Brownlee *et al*., 1986), the ability of this drug to improve cardiac compliance and decrease vascular hypertrophy has been demonstrated in animal models of hypertension, ageing and diabetes.

In this issue of *British Journal of Pharmacology*, Wu *et al*. demonstrate that treatment with aminoguanidine prevents

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detrimental changes of cardiac structure and function in a rat model of diabetes induced by streptozotocin and nicotinamide treatment that abolishes insulin secretion. Using an integrated mathematical model of elastance resistance, the authors inferred a significant decline in myocardial contractility associated with an increased internal resistance of the left ventricle in diabetic animals. They also measured an increased arterial load imposed on the heart resulting in overall impairment of the mechanical properties of both the left ventricle and the vasculature. Administration of aminoguanidine to diabetic rats ameliorated this impairment of cardiac pumping mechanics and retarded the augmentation in arterial loads. Consequently, rats treated with aminoguanidine had improved cardiac function when compared with control rats, presumably related to a general improvement of myocardial structure and function. Thus, this study adds to the evidence that aminoguanidine may be effective in preventing cardiac hypertrophy and arterial stiffening in diabetic animals (Chang *et al*., 2006).

It is important to realize that a mechanistic interpretation of aminoguanidine's actions in terms of AGE inhibition in the study of Wu *et al*. is limited by the relative lack of specificity of aminoguanidine therapy. For example, in addition to inhibiting AGE formation, aminoguanidine also inhibits NOS. Moreover, high concentrations of aminoguanidine may slowly degrade to form hydrogen peroxide, leading to pro-oxidant actions. The complexity of the pharmacological activity of aminoguanidine extends to prevention of PKC translocation and activity, decreased reactive oxygen species production and lipid peroxidation in retinal cells and reduction of lipid peroxidation in streptozotocin diabetic rats (reviewed in Rahbar and Figarola, 2003). Therefore, the beneficial effects of aminoguanidine may be due to several interrelated mechanisms, in addition to a reduction of AGEs, that may all contribute to improvement of the diabetic myocardial dysfunction caused by hyperglycaemia.

Another important limitation of aminoguanidine therapy is that it may have toxic effects when used in humans. The failure of aminoguanidine to be successful in human clinical trials may be attributed to its rapid renal clearance, subliminal concentrations *in vivo* and its high chemical reactivity. In a large randomized, double-blind, placebo-controlled, multicentric trial (ACTION I), aminoguanidine therapy slowed the progression of nephropathy in patients with type I diabetes (Bolton *et al*., 2004). However, severe side effects, such as vasculitis and abnormalities in liver function, were reported in the companion study on type II diabetes (Freedman *et al*., 1999). Importantly, a variety of agents have been developed, including pyridoxamine and pyridoxamine analogues ALT-946, OPB-9195, benfotiamine, alagebrium chloride, *N*-phenacylthiazolium bromide and LR-90, that may have beneficial effects similar to aminoguanidine with a better safety profile. Moreover, reduction in accumulation of AGEs in diabetes may be achieved with a number of established safe therapies, including ACE inhibitors, angiotensin receptor antagonists, metformin and peroxisome proliferators receptor agonists. These results may be due to the effects of these conventional therapies to improve glucose tolerance and insulin resistance. At present, the clinical utility of AGE inhibition remains to be firmly established. Thus, optimal metabolic, blood pressure and diet control achieved in an early and sustained manner using conventional therapies remains the best recourse for inhibition of AGEs and prevention of diabetic cardiomyopathy in the clinical setting.

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