PPAR-γ agonists decrease hyperhomocysteinemia and cardiac dysfunction: new hope for ailing diabetic hearts?

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THE Peroxisome proliferator-activated receptor-γ (PPAR-γ) family of nuclear hormone receptors has been extensively studied due to its antidiabetic, anti-inflammatory, and antithrombotic actions. PPAR-γ heterodimerizes with the retinoid X receptor to regulate transcription of target genes by binding to specific peroxisome proliferator-response elements. Structurally diverse ligands activate PPAR-γ, including eicosanoids, 15-deoxy-D12,14-prostaglandin J2, and antidiabetic thiazolidinedione drugs, such as troglitazone, ciglitazone, pioglitazone, and rosiglitazone (18). PPAR-γ controls adipocyte differentiation and regulates the actions of insulin on adipose tissue and skeletal muscle (13). Therefore, ligands that activate PPAR-γ are widely used as insulin-sensitizing agents in treatment of noninsulin-dependent diabetes mellitus.

Increasing evidence suggests that PPAR-γ activators impact the cardiovascular system through not only their lipid- and carbohydrate-lowering effects but also their anti-inflammatory and antioxidant actions. In general, the effects of PPAR-γ agonists, such as pioglitazone, on HDL cholesterol and triglycerides are associated with their antiatherosclerotic actions, whereas the nonlipid effects on inflammatory cytokine production and oxidative stress are thought to underlie the ability of PPAR-γ agonists to lower blood pressure and improve endothelial dysfunction (see Ref. 20 for an excellent review). The metabolism-independent effects of PPAR-γ activators in the heart are somewhat more controversial. Sfrinich’s group (9) reported that the PPAR-γ activator pioglitazone has beneficial, long-term effects on cardiac hypertrophy and cardiac inflammation but had no effect on cardiac function in stroke-prone spontaneously hypertensive rats. A novel PPAR-γ agonist, 2-[2-(phenoxy-2-propylphenoxy)-ethyl]indole-5-acetic acid, had no effect on contractile function in Type 2 diabetic db/db mice despite improved insulin-stimulated glucose uptake, increased glucose oxidation, and decreased fatty acid oxidation (5). On the other hand, pioglitazone and rosiglitazone have been shown to improve left ventricular (LV) systolic and diastolic function in response to mitral valve regurgitation (15) and acute ischemia in nondiabetic pigs (24) and reduced cardiac fibrosis on DOCA-salt hypertensive rats (11).

In this issue of American Journal of Physiology-Heart and Circulatory Physiology, Rodriguez et al. (17) report that pioglitazone treatment of mice fed a high-fat diet improved diabetes-induced cardiac remodeling, contractile dysfunction, and hypertension. These beneficial effects were associated with reduced tissue (but not plasma) homocysteine (Hcy), decreased matrix metalloproteinase (MMP)-2/9 activation and expression, increased tissue nitric oxide (NO) production, and improved endothelial-myocyte coupling. Although this group (21) and others have linked reduction in plasma Hcy levels to PPAR-γ agonists (14), this is the first study to link PPAR-γ activation with reduction in cardiac tissue Hcy levels in a diabetic model. The reduction in tissue Hcy may represent an additional mechanism by which PPAR-γ activators improve structure and function in the ailing, diabetic myocardium. A recent study (19) of patients with Type 2 diabetes reported that increased plasma levels of Hcy were associated with increased incidence of ischemic heart disease, hypertension, and coronary artery disease. However, the study by Rodriguez et al. (17) suggests that decreased tissue levels of Hcy may have a more important influence than plasma Hcy levels on local properties of the diabetic myocardium, such as endothelial-myocyte coupling, chamber remodeling, and NO bioavailability. Hyperhomocysteinemia is linked to adverse cardiac remodeling and contractile dysfunction in both human and animal models. A recent prospective investigation (7) of hypertensive and normotensive patients in the Genetic and Environmental Factors in Coronary Atherosclerosis (GENICA) suggested that increased plasma levels of Hcy are inversely related to LV ejection fraction and directly predict increased cardiovascular mortality in patients with high-risk coronary artery disease hypertension. Tyagi’s group (6) has already reported that Hcy mediates cardiac remodeling and disruption of endothelial myocyte coupling in the two-kidney, one-clip Goldblatt hypertensive mouse model and extracellular matrix (ECM) remodeling in homocysteinemic obese rabbits. Moreover, daily injections of Hcy for 14 days in normal rats significantly decreased posterior wall thickness, increased LV in diastolic and systolic dimensions, and decreased fractional shortening (23).

Another important observation in the Rodriguez et al. (17) study is that diabetes-induced diastolic dysfunction [decreased first derivative of pressure (−dP/dt)] and reduced relaxation in response to acetylcholine and NO donors] was associated with endothelial-myocyte uncoupling. The modulatory effects of the endocardial and capillary endothelium on cardiac contractile function, growth, metabolism, and rhythmicity are well known (see Ref. 3 for a comprehensive review). The mechanisms that link Hcy and PPAR-γ agonists to improved LV remodeling and endothelial-myocardial coupling have not been extensively characterized. However, a common denominator may be endothelial dysfunction secondary to increased oxidative stress and reduced NO bioavailability. Indeed, Hcy increases the expression of the p22phox subunit of NAD(P)H oxidase in LV tissue as well as promoting assembly of the NAD(P)H oxidase subunits (2). This was related to an inhibition of NO-dependent regulation of cardiac oxygen consumption, which can be restored by antioxidants (2). The general paradigm appears to be that local, paracrine release of endothelium-derived NO, endothelin-1 (ET-1), and ANG II, prostaglandins, and endothelium-derived hyperpolarizing factor modulate the contractile properties of adjacent myocytes.

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In the present study (17), diabetes disrupted endothelium- and NO-dependent relaxation of isolated cardiac rings. These effects were associated with reduced tissue NO levels and increased tissue Hcy. Furthermore, pioglitazone reduced Hcy and improved endothelial-myocyte coupling. Because Hcy reduces NO bioavailability secondary to increased oxidative stress, it is tempting to speculate that Hcy is responsible for the diminished diastolic relaxation observed in response to diabetes. Data from Hart’s group suggest that PPAR-γ ligands enhance endothelial NO release (4) and may increase NO bioavailability by suppressing NAD(P)H oxidase as well as enhancing Cu/Zn-SOD activity and expression in endothelial cells (10). Given that Hcy exerts similar actions on the NAD(P)H oxidase (1, 2), it is likely that at least some of the antioxidant effects of PPAR-γ may result from reduced Hcy levels. In addition, the reduced response to the NO donor in diabetic LV rings suggests that mechanisms other than NO bioavailability may be involved, such as alterations in NO-dependent signaling mechanisms, including cGMP. Further studies are warranted to determine the causal relationships among Hcy, diabetes, and endothelial function.

The role of Hcy in diabetes-induced systolic dysfunction is less clear. In the study by Rodriguez et al. (17), diabetes-induced decreases in fractional shortening and +dp/dt were corrected by pioglitazone treatment. These effects may be due to direct effects on contractility due to increased intracellular Ca2+ concentrations or enhanced excitation-contraction coupling or indirect effects due to afterload reduction because pioglitazone decreases mean arterial pressure. In addition, alterations in systolic function by pioglitazone may not only be endothelium dependent but also NO independent as suggested by Kennedy et al. (12). It is tempting to speculate that ET-1 may be involved in these negative inotropic actions of Hcy, because it has been shown that Hcy decreases ET-1 release (20).

Another interesting finding is that pioglitazone reduced the increased levels and activity of MMP-2/9 that were observed in diabetic hearts. Similar results with PPAR-γ ligands for MMP-1 were observed in cardiac fibroblasts during ischemia-reperfusion (8) and for MMP-2/9 in macrophages and monocytes (16). The links among PPAR-γ activation, MMP-2/9 activation, and ECM remodeling in the present study are somewhat circumstantial, although increased MMP activity was associated with decreased wall thickness, suggesting ECM degradation, and no changes in interstitial and perivascular collagen were assessed. This is an important issue, because previous work by Tyagi’s laboratory promotes a role for local ECM remodeling and oxidation in diabetes-induced defects in endothelial-myocyte coupling in diabetes (22). The mechanisms that link PPAR-γ-dependent decreases in MMP-2/9 in the diabetic myocardium were also not studied. An attractive candidate would be the reduction in tissue Hcy levels. Hyperhomocysteinemia increases MMP-2/9 in diabetic cardiomyopathy (22) in hypertensive myocardium (21).

In summary, this intriguing study by Rodriguez et al. (17) suggests a possible link between reduced Hcy levels and the beneficial effects of PPAR-γ activation on diabetes-induced cardiac remodeling and contractile dysfunction. However, this study also raises several important questions. Other diabetic models without a high-fat diet must be considered to exclude the effects of pioglitazone on lipid metabolism. A direct role for Hcy in PPAR-γ actions remains to be established. Further studies must define the mechanisms by which PPAR-γ activators reduce LV tissue levels of Hcy in diabetes and the molecular pathways that mediate Hcy-induced endothelial-myocyte uncoupling.

REFERENCES