Editorial Commentary

Peroxisome Proliferator–Activated Receptors Ligands, Oxidative Stress, and Cardiac Fibroblast Extracellular Matrix Turnover

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The development of muscle hypertrophy and the excess deposition of extracellular matrix (ECM) proteins (ie, myocardial fibrosis) frequently accompany pathological cardiac remodeling. Peroxisome proliferator–activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear factor receptor superfamily. Three different PPARs have been identified to date (PPARα, PPARβ, and PPARγ). PPARs are endogenously activated by ligands such as fatty acids and eicosanoids. PPARs are known to modulate gene expression for pathways involved in fat, lipid and glucose metabolism, inflammation, cell cycle, and immune responses. The genetic manipulation in mice of PPARs can lead to the modulation of cardiac muscle hypertrophy. The experimental use of PPAR ligands has also demonstrated their capacity to ameliorate myocardial fibrosis. However, the effect of PPAR activation on modulating cardiac fibroblast (CF) ECM turnover has not been explored. PPARγ can be activated by small molecules such as glitazones and lead to decreases in glucose and lipid serum levels. These properties of glitazones have been used for the treatment of type 2 diabetes patients for which benefits are derived not only from their ability to enhance insulin sensitivity but to ameliorate development of atherosclerosis.

Glitazone derivatives such as rosiglitazone have also been shown to reduce myocardial infarct size after coronary artery occlusion–reperfusion. Evidence of improved contractile function and reduced levels of markers/mediators of inflammation accompanied the reduction in infarct size. Shiomi et al showed that long-term postmyocardial infarction treatment of mice with pioglitazone led to an amelioration of adverse left ventricular remodeling, improved contractile function, reduced levels of proinflammatory cytokines, compensatory hypertrophy, and interstitial fibrosis.

Angiotensin II (Ang II), a known pathological modulator of cardiac remodeling, has been shown to enhance production of reactive oxygen species (ROS) via stimulation of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase. Recent studies have proposed that stimulation of ROS production by Ang II may constitute a means by which this humoral factor contributes to development of tissue injury in organs such as blood vessels, kidney, and the heart. Enhanced production of ROS is also known to occur with hyperglycemia, and it is also thought to mediate organ damage in diabetes. Recent experimental studies have also demonstrated the capacity of high glucose conditions to stimulate the production of Ang II, hinting at the possible existence of positive feedback loops for ROS generation. Thus, uncontrolled diabetic patients may be at high risk of ROS-mediated organ damage.

The CF is the most abundant cell type present in the myocardium. The CF is responsible for synthesis and deposition of the majority of ECM proteins present in the myocardium, including collagen types I and III. The CF is also capable of synthesizing enzymes that degrade ECM proteins such as matrix metalloproteinases (MMPs). We and others have demonstrated that treatment of CF with Ang II is capable of stimulating ECM protein production and diminish its degradation. These effects appear dependent on the activation of Ang II type 1 (AT1) receptors because losartan is able to block them. Traditionally, these effects have been linked to the ability of Ang II to activate classical pathways associated with AT1 signaling such as inositol phosphate turnover. However, Sano et al reported recently that Ang II is capable of increasing intracellular ROS in CFs and that these increases can be inhibited by AT1 blockers and by nicotinamide-adenine dinucleotide/NADPH oxidase inhibitors. Thus, Ang II–induced ROS-linked signaling has emerged as a possible pathway to mediate the effects of this humoral factor on CF ECM turnover.

Published studies have shown that glitazones can attenuate the expression or activity of NADPH oxidase subunits. In a study by Dobrian et al, it was demonstrated that the expression of the NADPH oxidase subunits p47phox and gp91phox was reduced in obese rats by pioglitazone treatment, leading to decreased levels of ROS generation. These observations led the group of Mehta et al to propose the possibility that glitazones may have the capacity to diminish ROS generation induced by proinflammatory factors such as Ang II and tumor necrosis factor-α. Results from studies using endothelial cells treated with pioglitazone yield diminished levels of ROS generation when exposed to these proinflammatory agents. These data suggest that Ang II, which stimulates production of ECM proteins in CF, may signal, at least in part, by the generation of ROS species. Furthermore, glitazones, through their capacity to reduce the

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In this issue of Hypertension, Chen et al provide experimental evidence for the capacity of pioglitazone treatment to attenuate Ang II–induced increases in ROS generation. Ang II treatment also led to activation of the redox-sensitive transcription factor nuclear factor κB, and this effect was blocked by pioglitazone. More important, pioglitazone treatment was able to revert the profibrotic effects of Ang II on CF, which included enhanced production of type I collagen and suppressed expression and activity of MMPs. Supportive evidence for the role of ROS in mediating the profibrotic effects of Ang II was also derived from effects of the water soluble form of the antioxidant vitamin E (trolox), which led to similar effects as those derived from pioglitazone treatment. These results should be interesting to the clinician for various reasons. The first relates to the fact that glitazones continue to emerge as viable treatment options for type 2 diabetic patients. As discussed above, the main reason why they are considered serious options for treatment is that they enhance insulin sensitivity and reduce risk factors associated with development of atherosclerosis. However, with the increased incidence of diabetes present in the developed world in the younger population, a serious problem is emerging: that of a diabetic cardiomyopathy (DCM). DCM is characterized by a myocardial remodeling pathology that evolves in the absence of discernible vascular (ie, ischemic) involvement. An important component of the structural alterations observed in DCM myocardium is that of the enhanced deposition of ECM proteins (ie, fibrosis) yielding significant alterations in diastolic function. It is interesting to postulate that the use of glitazones may be further justified in diabetic patients given their apparent ability to act as antioxidants, which may ultimately diminish the deposition of ECM proteins in the myocardium.

A second important implication derived from these data are that patients at risk of developing enhanced ROS damage such as diabetics may benefit from the use of AT1 blockers in their treatment. Indeed, recent experimental observations indicate that the early use of AT1 blockers significantly decreases organ damage associated with hyperglycemia. Interestingly, the AT1 blocker losartan has also been associated with nonreceptor-mediated effects that may further validate its use. It has also been proposed that for patients at high risk of developing diabetes, an early prophylactic treatment with AT1 blockers to diminish ROS-mediated organ damage may be indicated.

In spite of the interesting observations derived from the study by Chen et al, many questions remain unanswered and are worthy of further investigation. Further direct evidence linking glitazones to their potential antioxidant properties is needed. The rigorous verification of such properties would further validate their use in conditions in which ROS generation is a significant mediator of organ damage. The molecular mechanism(s) underlying the capacity of pioglitazone to act as an antioxidant in CF was not identified in the study by Chen et al; thus, further work in this area is merited. Altogether, the clinical use of glitazones appears even more promising in light of these emerging properties of the compounds.

References
