Regulating PPARδ signaling as a potential therapeutic strategy for skeletal muscle disorders in heart failure

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Despite remarkable improvements in cardiac mortality rates during the past decades (4), poor quality of life remains a major concern for patients with heart failure. One of the determinants of quality of life is exercise tolerance (6). Limited exercise capacity can result from multiple abnormalities in heart failure, which include changes in intramuscular metabolism (20, 21, 28, 46), local inflammatory response (35), vascular endothelial dysfunction (9), insulin resistance (38), and altered nervous activities (15, 26).

Interestingly, considerable evidence now suggests a lack of correlation between impaired left ventricular ejection fraction and exercise performance in heart failure (11, 16, 24). The degree of left ventricular systolic dysfunction does not always explain the degree of exercise intolerance and fatigue. Thus recent interest has focused more on peripheral maladaptation of intrinsic metabolism in skeletal muscle that contributes to exercise intolerance in heart failure (22, 35, 41). Skeletal muscle disorder in heart failure is characterized by a shift from an oxidative to a more glycolytic phenotype (40). Anaerobic metabolism along with muscular acidosis and phosphocreatine depletion can result in the early onset of fatigue leading to exercise limitation (19, 46). However, molecular mechanisms underlying these peripheral effects remain largely unknown.

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor family of ligand-activated transcription factors. Three members of the PPAR family, PPARα, PPARδ, and PPARγ, are well known to form heterodimers with the retinoid X receptor and bind to peroxisome proliferator response element (PPRE) regulating the expression of target genes (42). The activation of PPARs modulates numerous biological processes. On the basis of the results obtained in human and animal studies, it appears that PPARδ mediates metabolic responses under multiple pathological conditions (3, 17, 30). PPARδ deficient mice are prone to weight gain on a high-fat diet (44), while the PPARδ transgenic line is protected against obesity and lipid accumulation (39). PPARδ is induced in skeletal muscle after exercise (36), and overexpression of constitutively active PPARδ in skeletal muscle causes an increase in oxidative muscle fibers, enhancing running endurance in mice (45).

GW501516, a synthetic molecule, is a PPARδ selective ligand when used at nanomolar concentrations (29). Recently, GW501516 has drawn a lot of attention, since GW501516 has been shown to be an exercise mimetic, which remodels skeletal muscle in exercise-trained mice (25). GW501516 and exercise training synergistically increase oxidative myofibers and enable mice to run 70% longer and further by a transcriptional activation of PPARδ (25).

Exercise training is one of the most effective ways to improve quality of life in heart failure patients. Regular physical exercise can partially improve peripheral metabolism in patients with chronic heart failure, because aerobic training activates mitochondrial aerobic enzymes in skeletal muscle (1, 23, 27, 37). Even in patients with advanced heart failure, the benefits of exercise training are present, including augmented regenerative capacity of circulating progenitor cells, enhanced endothelial function, and skeletal muscle neovascularization (8). Given the fact that physical exercise training can improve skeletal muscle impairments in heart failure (37) and that a PPARδ agonist GW501516 is an exercise mimetic (25), the missing link here is whether treatment with GW501516 results in favorable modulations of skeletal muscle metabolism in heart failure.

In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Zizola et al. (47) provide novel evidence demonstrating that a PPARδ agonist GW501516 restores skeletal muscle metabolism and improves exercise tolerance in a mouse model of ischemic left ventricular dysfunction. With their studies, they demonstrate that left ventricular dysfunction following myocardial infarction causes impaired exercise endurance in mice, which is accompanied by decreases in muscle fatty acid oxidation rates and ATP content, and an increase in gene expression of proinflammatory TNF-α in skeletal muscle. In vitro experiments demonstrate that TNF-α inhibits fatty acid oxidation in myocytes, yet treatment with GW501516 can reverse this inhibitory effect. Furthermore, the authors provide in vivo evidence that GW501516 reverses the left ventricular dysfunction-induced decrease in fatty acid oxidation in peripheral muscle, which enables mice to run longer and further, along with transcriptional changes including increased carnitine palmitoyltransferase I (CPT1) expression, a mitochondrial enzyme responsible for fatty acid transport (14). This study provides an important insight regarding the missing link between PPARδ signaling and exercise capacity in heart failure, and suggests the exciting possibility of a novel therapeutic approach using pharmacological activation of PPARδ for the progressive skeletal muscle dysfunction under the condition of cardiac dysfunction.

In some ways, this fascinating study by Zizola et al. provokes more questions than it answers regarding the physiological mechanisms underlying skeletal muscle abnormalities in heart failure. For instance, an important question crucial to the design of effective therapies remains: whether preventing an adaptive physiological response, such as a shift in myosin heavy chain fiber type from oxidative toward more glycolytic fibers, can be beneficial even under the hypoxic conditions due to advanced heart failure. Under severe left ventricular dys-
function, oxygen delivery to peripheral muscles can be limited as a result of reduced blood supply or reduced oxygen levels in the blood. This may cause a decrease in oxidative enzyme activities (13) and a shift of metabolism to anaerobic glycolysis as a compensatory mechanism. The adaptive response may yield less ATP than does complete oxidative metabolism, but saves the oxygen demand in skeletal muscle. If PPARδ agonists mediate a shift back to fatty acid oxidation under the limited oxygen availability, they may disturb the long-term balance between supply and demand of oxygen in peripheral tissues.

Secondarily, tumor necrosis factor (TNF-α) was first demonstrated to be linked with the beneficial effects of GW501516 on skeletal muscle metabolism based on in vitro findings in this study, but the following in vivo experiments showed no effects on TNF-α mRNA levels in skeletal muscle. However, GW501516 may be associated with functions of circulating TNF-α or soluble TNF receptors that mediate the TNF-α signaling in skeletal muscle, rather than local gene expression in myocytes. TNF-α that originates from the failing heart or activated macrophages (31) may lead to a detrimental effect on several signaling processes in skeletal muscle (18). Thus the pathophysiological implications of the TNF system provided by Zizola et al. are exciting as a potential mechanism by which PPARδ signaling improves exercise endurance in heart failure.

Third, although not addressed by the present study, potential benefits of PPARδ signaling for the skeletal muscle abnormalities may include vascular function. Skeletal muscle vasodilation contributes to the overall regulation of exercise hyperemia. GW501516 increases production of tetrahydrobiopterin (BH4), a cofactor of endothelial nitric oxide synthase (eNOS) in endothelial progenitor cells (12). PPARδ activation modulates endothelial progenitor cells and enhances angiogenesis in skeletal muscle of ischemic limbs (10, 34). Thus it is possible that the benefits that GW501516 exerts in skeletal muscle could involve the effects of increased microcirculation in limbs.

Last, the present study shows no beneficial effects of GW501516 on cardiac dysfunction following myocardial infarction. However, resting cardiac function may not always reflect the cardiac function during exercise. PPARδ has been demonstrated to regulate cardiac metabolism and limit myocardial inflammation and hypertrophy (2). Cardiomyocyte-specific deletion of PPARδ decreases basal myocardial fatty acid oxidation and increases oxidative damage, leading to congestive heart failure (5, 43). PPARδ activation by GW501516 prevents palmitate-induced ER stress (32), and exerts an antioxidative role in cardiomyocytes (33). This raises the question as to whether stimulating PPARδ signaling may improve cardiac functional reserve during exercise.

Emerging data suggest that PPARδ activation is an important regulator of skeletal muscle metabolism and is involved in exercise adaptations (7, 25). The work by Zizola et al. demonstrates that a PPARδ agonist is potentially a unique therapeutic approach to ameliorate left ventricular dysfunction-mediated deficits in skeletal muscle strength and function. Further studies will provide a rationale to focus on controlling peripheral metabolism by activating PPARδ as a therapeutic target for the treatment of muscle disorders in heart failure.

**REFERENCES**

PPAR6 FOR SKELETAL MUSCLE DISORDERS IN HEART FAILURE


