Reactivation of Peroxisome Proliferator-activated Receptor α Is Associated with Contractile Dysfunction in Hypertrophied Rat Heart*

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In pressure overload-induced hypertrophy, the heart increases its reliance on glucose as a fuel while decreasing fatty acid oxidation. A key regulator of this substrate switching in the hypertrophied heart is peroxisome proliferator-activated receptor α (PPARα). We tested the hypothesis that down-regulation of PPARα is an essential component of cardiac hypertrophy at the levels of increased mass, gene expression, and metabolism by pharmacologically reactivating PPARα. Pressure overload (induced by constriction of the ascending aorta for 7 days in rats) resulted in cardiac hypertrophy, increased expression of fetal genes (atrial natriuretic factor and skeletal α-actin), decreased expression of PPARα and PPARα-regulated genes (medium chain acyl-CoA dehydrogenase and pyruvate dehydrogenase kinase 4), and caused substrate switching (measured ex vivo in the isolated working heart preparation). Treatment of rats with the specific PPARα agonist WY-14,643 (8 days) did not affect the trophic response or atrial natriuretic factor induction to pressure overload. However, PPARα activation blocked skeletal α-actin induction, reversed the down-regulation of measured PPARα-regulated genes in the hypertrophied heart, and prevented substrate switching. This PPARα reactivation concomitantly resulted in severe depression of cardiac power and efficiency in the hypertrophied heart (measured ex vivo). Thus, PPARα down-regulation is essential for the maintenance of contractile function of the hypertrophied heart.

Pressure overload of the heart activates a complex series of interconnected signaling cascades resulting in adaptive responses for the maintenance of a normal cardiac output (1, 2). This adaptation includes alterations in cardiomyocyte mass (trophic response), gene expression, and metabolism (1–6). At the trophic level, the heart hypertrophies (1, 7). At the transcriptional level, the heart reexpresses fetal genes (such as atrial natriuretic factor (ANF)† and skeletal α-actin) while depressing the expression of various adult isoforms (e.g. cardiac α-actin) (4, 8). At the level of metabolism, the hypertrophied heart increases reliance on glucose as a fuel and depresses fatty acid oxidation (the dominant energy source for the normal heart) (5, 6, 9).

A key regulator of substrate switching in the heart is postulated to be PPARα (10). This nuclear receptor regulates the expression of several genes involved in both fatty acid and glucose oxidation. These include the fatty acid transporter (FAT/CD36), fatty acid-binding protein, malonyl-CoA decarboxylase, muscle-specific carnitine palmitoyltransferase I, medium and long chain acyl-CoA dehydrogenases, as well as pyruvate dehydrogenase kinase 4 (11–16). For example, increased fatty acids in the diabetic milieu result in activation of PPARα, induction of PPARα-regulated genes, and increased fatty acid oxidation with depression of glucose oxidation (17, 18). In contrast, increased reliance of the hypertrophied heart on glucose as a fuel is associated with decreased PPARα expression and DNA binding activity (10, 19). Despite these observations, no study has directly linked substrate switching of the heart with altered PPARα activity.

Metabolism and contractile function of the heart are closely linked. We therefore set out to test the hypothesis that substrate switching in response to pressure overload was essential for the development of a hypertrophied heart that was able to maintain cardiac output. This hypothesis was tested by pharmacologically reactivating PPARα in the hypertrophied heart through treatment of rats with the specific PPARα agonist WY-14,643. Treatment of rats with WY-14,643 did not affect the trophic response or induction of ANF in response to pressure overload. However, PPARα activation prevented skeletal α-actin induction, reversed the down-regulation of measured PPARα-regulated genes in the hypertrophied heart, and prevented substrate switching. This PPARα reactivation concomitantly resulted in severe depression of cardiac power and efficiency in the hypertrophied heart. Therefore, down-regulation of PPARα in response to pressure overload is essential for the maintenance of contractile function of the hypertrophied heart.

EXPERIMENTAL PROCEDURES

Animals—Male Sprague-Dawley rats (initial weight, 225 g) were kept in the Animal Care Center of the University of Texas-Houston Medical School under controlled conditions (23 ± 1 °C; 12-h light/12-h dark cycle) and received standard laboratory powdered chow (Purina) and water ad libitum. Two interventions were utilized in the present study, pressure overload-induced hypertrophy (through banding of the ascending aorta) and chronic PPARα activation (through feeding animals the specific PPARα agonist WY-14,643 in powdered chow at a concentration of 0.01% w/w). On day −1, animals were initiated on the powdered diet with or without added agonist (agonist group and control group, respectively). These diets were maintained throughout the

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† The abbreviations used are: ANF, atrial natriuretic factor; PPARα, peroxisome proliferator-activated receptor α; S/C, sham/control; B/C, banded/control; S/A, sham/agonist; B/A, banded/agonist.
course of the study (a total of 8 days). On day 0, animals underwent surgery and were randomly divided into one of four groups: 1) sham/control (S/C) group, 2) banded/control (B/C) group, 3) sham/agonist (S/A) group, and 4) banded/agonist (B/A) group. On day 7, animals were anesthetized, and hearts were isolated and either perfused (for *ex vivo* metabolic and functional investigations) or frozen (for gene expression determination).

Heart Perfusions—Isolated hearts were perfused using the working heart preparation as described previously (20). Hearts were initially perfused in the Langendorff mode with Krebs-Henseleit buffer containing 5 mM t-glucose, followed by a 30-min nonrecirculating perfusion in the working mode with Krebs-Henseleit buffer containing 5 mM t-glucose (plus 20 μCl/μl [U-14C]glucose), 0.5 mM sodium l-lactate (plus 2 μCl/μl [U-14C]lactate), 0.05 mM sodium l-tyrosine, and 0.4 mM sodium oleate (plus 30 μCl/μl [9,10-3H]oleate) bound to 3% bovine serum albumin (fraction V, fatty acid free; Interchek, Purchase, NY) and 40 micromol/ml insulin (Lilly). After 30 min of perfusion (15 cm H2O preload/100 cm H2O afterload), hearts were freeze-clamped and stored in liquid nitrogen before dry weight determination. Rates of oleate oxidation, carbohydrate oxidation (combination of exogenous glucose and lactate oxidation), and oxygen consumption, as well as cardiac power and efficiency, were determined as described previously (20).

RNA Extraction and Quantitative Reverse Transcription-Polymerase Chain Reaction—RNA extraction and quantitative reverse transcription-polymerase chain reaction of samples were performed using previously described methods (8, 21, 22). Quantitative specific assays were designed from rat sequences available in GenBank™. Primers and probes were designed from nonconserved sequences of the genes (allowing for isoform specificity), spanning sites where two exons join (splice sites) when such sites are known (preventing recognition of the assay to any potential contaminating genomic DNA). Standard RNA was made for all assays by the T7 polymerase method (Ambion, Austin, TX), using total RNA isolated from the rat heart. The correlation between the Ci (the number of polymerase chain reaction cycles required for the fluorescent signal to reach a detection threshold) and the amount of standard was linear over at least a 5-log range of RNA for all assays (data not shown). The level of transcripts for the constitutive housekeeping gene product cyclophilin was quantitatively measured in each sample to control for sample-to-sample differences in RNA concentration. Polymerase chain reaction data are reported as the number of transcripts/1000 cycles.)

Statistical Analysis—Data are presented as the mean ± S.E. Statistically significant differences between groups were calculated by the Student’s t test. A value of p < 0.05 was considered significant.

RESULTS

Trophic and Gene Expression Markers of Hypertrophy—One week after the initial ascending aortic constriction, the heart weight and the heart weight/body weight ratio both increased, with no effect on body weight (Table I). This trophic response was also observed when pressure overload was induced in animals that were treated with the PPARα agonist (Table I). The agonist alone had no effect on any of these parameters (Table I).

Pressure overload is known to induce the expression of several fetal genes, including ANF and skeletal α-actin. There was a 2.4- and 2.3-fold induction in the steady-state levels of ANF and skeletal α-actin mRNAs, respectively, in response to pressure overload (Fig. 1). Although ANF was also increased in the B/A group, induction of skeletal α-actin in response to pressure overload was severely attenuated by the agonist (Fig. 1). The agonist alone had no effect on either ANF or skeletal α-actin expression (Fig. 1).

Expression of PPARα and PPARα-regulated Genes—We investigated the effects of both pressure overload and chronic PPARα activation on the mRNA levels of PPARα and the PPARα-regulated genes, medium chain acyl-CoA dehydrogenase and pyruvate dehydrogenase kinase 4. Pressure overload significantly reduced cardiac PPARα mRNA as well as medium chain acyl-CoA dehydrogenase mRNA (Fig. 2). The effect of pressure overload on pyruvate dehydrogenase kinase 4 expression did not reach significance. Treatment of rats with WY-14,643 increased the expression of both medium chain acyl-CoA dehydrogenase and pyruvate dehydrogenase kinase 4, with no effect on PPARα expression (Fig. 2). The mRNA levels of medium chain acyl-CoA dehydrogenase and pyruvate dehydrogenase kinase 4 in the banded/agonist group were between those observed in the banded/control and sham/agonist groups (Fig. 2).

Oxygen Consumption and Substrate Switching—We investigated the effects of reactivation of PPARα on oxygen consumption and substrate selection in the hypertrophied heart *ex vivo*, using the isolated working heart preparation. The induction of hypertrophy or treatment of animals with WY-14,643 alone had no effect on oxygen consumption (Fig. 3A). In contrast, the two interventions in combination resulted in a significant reduction in oxygen consumption (Fig. 3A).

Treatment of rats with WY-14,643 alone had no significant effects on either oleate or carbohydrate (glucose plus lactate) oxidation (Fig. 3, B and C). Aortic constriction had reciprocal effects on the rates of oleate and carbohydrate oxidation, although these effects did not reach statistical significance (Fig. 3, B and C). In contrast, the two interventions together tended to reduce the rates of both oleate and carbohydrate oxidation (Fig. 3, B and C).

To determine substrate selection of the perfused hearts, the contribution of oleate and carbohydrate oxidation to total oxygen consumption was calculated. This calculation enables substrate selection to be determined, taking into account any changes in oxygen consumption (which is affected by both cardiac efficiency and cardiac work/output). Under our perfusion conditions, the normal heart has a 47% reliance on oleate as a substrate and a 19% reliance on carbohydrate oxidation, whereas the remaining 34% is presumably due to endogenous substrate oxidation (intracellular glycogen, fatty acids, and lipids). The agonist alone had no effect on substrate selection (Fig. 4). Hypertrophy was associated with a decrease in relative oleate oxidation and a reciprocal increase in carbohydrate oxidation (Fig. 4). This substrate switching of the hypertrophied heart was completely abolished in the presence of the agonist (Fig. 4).

Cardiac Power and Efficiency—Cardiac power was determined for all perfused hearts. The hypertrophied hearts were able to maintain the same cardiac power as normal hearts (Fig. 5A). In addition, treatment of rats with the agonist had no effect on cardiac power (Fig. 5A). In contrast, chronic activation of PPARα in the hypertrophied heart resulted in a dramatic decrease in cardiac power (Fig. 5A). A similar pattern was observed for cardiac efficiency (Fig. 5B), which was significantly altered in the banded/agonist group (decreased by 52% compared with agonist alone; S/A versus B/A).

DISCUSSION

The present study investigated whether the down-regulation of PPARα is essential for the development of a hypertrophied heart that was able to maintain cardiac output in response to...
pressure overload. Specifically, we investigated growth, gene expression, function, and metabolism of the hypertrophied heart in which PPARα was chronically reactivated pharmacologically. Pressure overload resulted in an increase in cardiac mass, reexpression of fetal genes, decreased expression of PPARα and PPARγ-regulated genes, and increased reliance on carbohydrate oxidation (while depressing fatty acid oxidation), enabling maintenance of contractile function (as compared with a normal heart). Chronic reactivation of PPARα in the hypertrophied heart had no effect on the trophic response or the induction of ANF mRNA in response to pressure overload. However, reactivation of PPARα in the hypertrophied heart prevented the induction of skeletal α-actin mRNA, increased the expression of PPARα-regulated genes to levels comparable with those observed in the normal heart, and prevented substrate switching. This resulted in a concomitant severe depression of cardiac power and efficiency. The results suggest that down-regulation of PPARα is essential for pressure overload-induced substrate switching in the heart and maintenance of cardiac function.

Adaptation to Pressure Overload—Pressure overload induces the activation of multiple signaling cascades involved in the development of hypertrophy (1–3). This adaptation, which occurs at various levels (trophic, gene expression, and metabolic levels), allows the maintenance of cardiac function in the face of increased pressure.

At the trophic level, the cardiomyocyte size increases (hypertrophy), a process requiring increased protein synthesis (1). Chronic reactivation of PPARα in the hypertrophied heart had no effect on the trophic response or the induction of ANF mRNA in response to pressure overload. However, reactivation of PPARα in the hypertrophied heart prevented the induction of skeletal α-actin mRNA, increased the expression of PPARα-regulated genes to levels comparable with those observed in the normal heart, and prevented substrate switching. This resulted in a concomitant severe depression of cardiac power and efficiency. The results suggest that down-regulation of PPARα is essential for pressure overload-induced substrate switching in the heart and maintenance of cardiac function.
hypertrophied heart. This includes those genes encoding for contractile proteins, signaling proteins, transcription factors, metabolic enzymes, and structural proteins. Commonly reported gene expression markers for the hypertrophied heart include the reexpression of various fetal genes, including ANF, skeletal α-actin, and myosin heavy chain (8). In the case of the latter two fetal genes, the expression of the adult isoforms is decreased (cardiac α-actin and myosin heavy chain, respectively) in the hypertrophied heart (8). The molecular mechanisms involved in altered expression of these genes are complex and have not been elucidated fully, but some overlap exists with the mechanisms involved in the trophic response (with the exception of phosphatidylinositol 3-kinase and p70S6K, which appear to be exclusive for the growth response) (3, 4, 28).

At the level of metabolism, the hypertrophied heart decreases its reliance on fatty acids as a major substrate for ATP generation while increasing its reliance on glucose as a fuel (5, 6). Although the exact mechanism for this substrate switching is not known, the transcription factor PPARα is a strong candidate to play a role. The hypertrophied heart possesses decreased expression of several genes encoding for key proteins involved in fatty acid metabolism (e.g. FAT/CD36, fatty acid-binding protein, malonyl-CoA decarboxylase, muscle-specific carnitine palmitoyltransferase I, medium chain acyl-CoA dehydrogenase, and long chain acyl-CoA dehydrogenase) (10, 15). Many of these genes are regulated by PPARα, which has been shown to be down-regulated (both transcriptionally and post-transcriptionally) in the hypertrophied heart (19).

**Role of PPARα in Cardiac Adaptation**—We set out to investigate the role of decreased PPARα in the development of the hypertrophied heart in response to pressure overload. Such a study would help to clarify several questions. First, is decreased PPARα essential for substrate switching in the hypertrophied heart? Second, does decreased PPARα play a role, either directly or indirectly (through substrate switching for example), in the trophic and/or gene expression changes observed in response to pressure overload? And third, is decreased PPARα essential for the maintenance of contractile function of the hypertrophied heart?

Consistent with previously published studies, our results show that pressure overload results in substrate switching by the heart (i.e. decreased reliance on oleate and increased reliance on carbohydrate). The observed decrease in medium chain acyl-CoA dehydrogenase expression is consistent with decreased rates of fatty acid oxidation, whereas the decrease in pyruvate dehydrogenase kinase 4 expression is consistent with increased rates of carbohydrate oxidation. Chronic activation of PPARα completely blocked this substrate switching (and the decreases in medium chain acyl-CoA dehydrogenase and pyruvate dehydrogenase kinase 4 expression) in the pressure-overloaded heart, suggesting that decreased PPARα is indeed an essential component for substrate switching.
Pressure overload resulted in both an increase in the heart weight/body weight ratio and a reactivation of fetal genes (ANF and skeletal α-actin). It is possible that decreased expression (and DNA binding activity) of the nuclear factor PPAR plays a role in either the trophic or gene expression responses of the heart to pressure overload, either directly (by binding to promoter regions of fetal genes) or indirectly. In the latter case, substrate switching induced by decreased PPAR could alter metabolites in the cell that might potentially affect the activity of various transcription factors. Recent work in our laboratory suggests that glucose metabolites affect MHC isofrom gene expression in the heart. Chronic activation of PPARα did not prevent the induction of either the trophic response or the reexpression of ANF in response to pressure overload. However, in the case of skeletal α-actin, the reexpression of this fetal gene was abolished by chronic PPARα activation, suggesting that the gene encoding for this sarcomeric protein is influenced by the level of PPARα DNA binding activity. We hypothesize that substrate switching, as opposed to PPARα directly influencing the skeletal α-actin promoter, plays a role in the induction of this gene. Indeed, Sp1, a known glucose-regulated transcription factor, is essential for the induction of skeletal α-actin expression in the hypertrophied heart.

Hypertrophy is an adapted state, enabling the heart to maintain cardiac output in the face of pressure overload. Whether adaptation at all levels (trophic, gene expression, and metabolic levels) is essential for maintenance of cardiac function is unknown. By reactivating PPARα in the hypertrophied heart and thereby blocking substrate switching, we were able to show that the metabolic adaptation is essential. We chose to investigate cardiac function *ex vivo* (in the isolated working heart preparation) rather than *in vivo* (use of echocardiogram, for example) so that external influences, such as fuel and neurohumoral factors, are constant for all hearts. For example, WY-14,643 has been shown previously to have a lipid-lowering effect *in vivo*, which would then influence fuel availability for the heart (30). The results show that neither pressure overload nor WY-14,643 treatment alone has any significant effects on cardiac power or efficiency. However, when PPARα is reactivated in the hypertrophied heart, both cardiac power and efficiency decrease dramatically. Thus, down-regulation of PPARα is essential for the maintenance of cardiac output by the hypertrophied heart.

**Loss of Plasticity of the Hypertrophied Heart**—The hypertrophied heart is less able to adapt to subsequent changes in its environment. For example, the hypertrophied heart is more susceptible to reperfusion damage after an ischemic insult (31). In addition, the accumulative stress of diabetes on the hypertrophied heart leads to heart failure (32). In diabetes, plasma fatty acids are elevated, which are able to activate PPARα. It is therefore possible that increased PPARα activity in the hypertrophied heart within the diabetic milieu results in cardiac dysfunction, similar to that observed in the present study. This may explain the reported contractile dysfunction in the obese Zucker rat heart, a hypertrophic heart within a diabetic milieu (33, 34).

Hypertrophy precedes heart failure. The factors involved in the transition from hypertrophy to heart failure are not known. Because the failing heart has been described as energy-starved (35), much work from our laboratory has focused on alterations in metabolic control in both the hypertrophied and the failing heart. The present study suggests that substrate switching may be essential for the maintenance of cardiac output. We have recently found that in addition to decreased fatty acid metabolic gene expression, the failing human heart possesses decreased expression of both glucose transporters 1 and 4. Because increased glucose oxidation is essential for cardiac function in the face of pressure overload, decreased glucose transport in the cardiomyocyte may play a role in contractile dysfunction in the failing human heart.

**Limitations of the Study**—The present study has shown that reactivation of PPARα in the hypertrophied heart prevents substrate switching, with a concomitant depression of contractile function. We speculate that the prevention of substrate switching causes the contractile function in the face of pressure overload. However, the present study cannot rule out the possibility that these two observations are independent and that

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2 M. E. Young and H. Taegtmeyer, unpublished observations.

3 P. Razeghi, M. E. Young, and H. Taegtmeyer, unpublished observation.
the depression of cardiac performance was due to an additional effect of PPARα reactivation. For example, the induction of skeletal α-actin may be essential for contractile function, or the induction of additional PPARα-regulated genes that were not investigated in the present study may play a role in the observed contractile dysfunction. One such candidate is UCP3, which we have recently shown to be controlled by PPARα.

Conclusions—Reactivation of PPARα in the hypertrophied heart had no effect on the trophic response or the induction of ANF in response to pressure overload. In contrast, PPARα reactivation abolished skeletal α-actin induction, prevented substrate switching in the hypertrophied heart, and resulted in severe impairment of cardiac function. The results suggest that down-regulation of PPARα is essential for substrate switching and maintenance of cardiac function of the hypertrophied heart.

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