Peroxisome Proliferator–Activated Receptor α Gene Regulates Left Ventricular Growth in Response to Exercise and Hypertension

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Background—Left ventricular hypertrophy (LVH) occurs as an adaptive response to a physiological (such as exercise) or pathological (valvular disease, hypertension, or obesity) increase in cardiac work. The molecular mechanisms regulating the LVH response are poorly understood. However, inherited defects in fatty acid oxidation are known to cause severe early-onset cardiac hypertrophy. Peroxisome proliferator–activated receptor α (PPARα) regulates genes responsible for myocardial fatty acid oxidation and is downregulated during cardiac hypertrophy, concomitant with the switch from fatty acid to glucose utilization.

Methods and Results—The role of PPARα in left ventricular growth was investigated in 144 young male British Army recruits undergoing a 10-week physical training program and in 1148 men and women participating in the echocardiographic substudy of the Third Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg study. A G/C polymorphism in intron 7 of the PPARα gene significantly influenced left ventricular (LV) growth in response to exercise ($P=0.009$). LV mass increased by 6.7 ± 1.5 g in G allele homozygotes but was significantly greater in heterozygotes for the C allele (11.8 ± 1.9 g) and in CC homozygotes (19.4 ± 4.2 g). Likewise, C allele homozygotes had significantly higher LV mass, which was greater still in hypertensive subjects, and a higher prevalence of LVH in the Third MONICA Augsburg study.

Conclusions—We demonstrate that variation in the PPARα gene influences human left ventricular growth in response to exercise and hypertension, indicating that maladaptive cardiac substrate utilization can play a causative role in the pathogenesis of LVH. **(*Circulation*. 2002;105:950-955.)**

Key Words: genetics ■ hypertrophy ■ exercise ■ hypertension ■ fatty acids

Left ventricular hypertrophy (LVH) is generally understood to be an adaptive response to increased workload. In fact, both physiological and pathological stimuli (valvular disease, hypertension, obesity, and exercise[1]) may stimulate cardiac growth. In addition, mutations in genes encoding sarcomeric proteins affecting contractility may cause LVH.[2] LVH is an independent risk factor for cardiovascular morbidity and mortality[3,4] through largely unknown mechanisms. However, studies in related[5] and unrelated[6] individuals clearly demonstrate that a high proportion of interindividual variability in left ventricular mass and risk of LVH is attributable to genetic factors.[7]

An important molecular adaptation in the hypertrophied heart is the increase in glucose utilization and decrease in fatty acid oxidation (FAO) attributable to downregulation of FAO enzyme mRNA levels.[8] Defects in mitochondrial FAO enzymes cause childhood hypertrophic cardiomyopathy,[9] and perturbation of FAO in animal models causes cardiac hypertrophy,[10,11] indicating that substrate utilization is important in the pathogenesis of hypertrophy. Peroxisome proliferator–activated receptor α (PPARα) is a ligand-activated transcription factor[12] that regulates the expression of genes involved in fatty acid (FA) uptake and oxidation, lipid metabolism, and inflammation.[13] Ligands for PPARα include long-chain fatty

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acids[14] and the fibrate class of lipid-lowering drugs.[15] PPARα is expressed at high levels in tissues that catabolize FA, such as the liver, skeletal muscle, and heart.[16] PPARα regulates the expression of cardiac mitochondrial FAO enzymes[17] and is downregulated during cardiac hypertrophy in vitro and in vivo, leading to reduced FAO and impaired cellular lipid homeostasis.[18] PPARα-knockout mice have markedly reduced FAO and exhibit cardiac lipid accumulation and fibrosis[19] and die on inhibition of mitochondrial fatty acid uptake.[20]

The influence of PPARα on cardiac growth was examined using the previously described functional leucine 162 valine (L162V) variant[21] and a novel G/C polymorphism in intron 7 of the human PPARα gene. In particular, the role of PPARα in the physiological left ventricular hypertrophic response to exercise was examined in 144 young male British Army recruits undergoing an intense 10-week physical training program.[22] The role of PPARα in the pathophysiological response to hypertension was investigated in a population-based sample of 1148 German men and women participating in the Third Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg survey.[23]

Methods

Study Populations

The army exercise study comprises 144 healthy normotensive white male British Army recruits, selected for homozygosity of the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) genotype, randomized to receive placebo or 25 mg/d losartan, an AT_1 receptor antagonist, throughout a 10-week training program. Recruits underwent an identical standard supervised training regime consisting of mixed upper and lower body strength and endurance training. At the start and end of training, height, weight and blood pressure were determined and cardiac MRI was performed. Briefly, 10-mm ECG-gated short-axis cardiac images (single breath holding, 0.5T) were obtained, and left ventricular (LV) mass was determined by multiplying myocardial tissue volume by myocardial tissue-specific density. Chamber volumes were calculated by summing end-diastolic and end-systolic endocardial areas in each slice.[22] The effects of environmental variation are minimized by the racial, age, and sex homogeneity of the cohort, the absence of cardiorespiratory disease, identical living quarters and clothing, and access to a high-carbohydrate diet.

The echocardiographic substudy of the third MONICA Augsburg survey has been previously described.[23] Subjects originate from a sex- and age-stratified random sample of all German residents of the Augsburg study area aged 25 to 74 years. Hypertension was defined as systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥95 mm Hg or intake of antihypertensive medication during the 7 days preceding the examination. A 2-dimensionally guided M-mode echocardiogram was performed on each subject. Structures for M-mode–guided calculation of LVM were measured according to the guidelines of the American Society of Echocardiography, and LVM was calculated and indexed to body surface area as LVM index in g/m^2 of body surface area. LVH was defined when LVM index was >134 g/m^2 body surface area in men or >110 g/m^2 body surface area in women.

Genotype Determination

Genotyping was carried out by polymerase chain reaction (PCR) and restriction enzyme digestion. PPARα L162V and ACE I/D genotyping was performed as previously described.[21,22] Intron 7 genotyping was performed in NH_3 buffer (16 mmol/L $[NH_4]_2SO_4$, 67 mmol/L TRIS, pH 8.4, 0.01% Tween 20, 0.02 mmol/L each dNTP), 2 mmol/L $MgCl_2$, 8 pmol each primer, and 0.2 U *Taq* polymerase. PCR primers were forward ACAATCACTCCTTAAATATGGTGG and reverse AAGTAGGGACAGACAGGACCAGTA, generating a fragment of 266 bp. PCR products were digested with 3 U TaqI (Helena Biotech) for 4 hours at 65°C and analyzed using the microtiter array diagonal gel electrophoresis system.[24]

TABLE 1. Baseline Characteristics of Sample Populations

	British Army Recruits	Third Augsburg MONICA Study	
		Men	Women
Sample size	144 men	578	564
Age, y	19.6±2.4	50.3±13.7	50.7±13.3
BMI, kg/m^2	23.1±2.2	26.7±3.1	26.3±4.5
Systolic BP, mm Hg	117.9±11.7	136±18.6	130±20.5
Diastolic BP, mm Hg	66.1±10.6	82.7±11.6	78.6±11.3
Cholesterol, mmol/L	nd	233±43.5	232±44.2
PPARα V162 allele frequency	0.074	0.065	
(95% CI)	(0.043–0.105)	(0.055–0.075)	
PPARα intron 7 C allele frequency	0.181	0.179	
(95% CI)	(0.136–0.225)	(0.163–0.195)	

Values are mean±SD. BP, indicates blood pressure, and nd, not determined.

Statistical Analysis

Association between PPARα genotype and variables was analyzed using SPSS 6.1 statistical package and SAS 6.12 statistical software. Allele frequencies were determined by the gene-counting method. The effect of PPARα genotype at baseline and after training characteristics in BigHeart 2 was examined by ANOVA and multiple linear regression. The effect of intron 7 genotype in the Third MONICA Augsburg study was investigated by multiple linear regression with age, body mass index (BMI), sex (where necessary), systolic blood pressure, and antihypertensive medication in the models.

Results

The intron 7 polymorphism, originally reported as a TaqI RFLP,[25] was found by direct sequencing to be a G to C transversion at nt 2528 of intron 7 of the PPARα gene.

Effects in Response to Exercise

Intron 7 and L162V genotypes were determined in 144 young healthy male white British Army recruits, randomized to receive either low-dose Losartan or placebo. Losartan treatment did not affect LV growth.[22] Intron 7 C allele frequency was 0.181 (95%CI, 0.136 to 0.225), V162 allele frequency was 0.074 (95% CI, 0.043 to 0.105), and genotype distributions were in Hardy-Weinberg equilibrium (Table 1). At baseline, age, weight, BMI, systolic and diastolic blood pressure, and measures of heart size were not significantly different between genotypes (not shown). With 10 weeks of an intense training program, LV mass determined by cardiac magnetic resonance increased significantly by 8.6±1.2 g ($P<0.0001$). This increase in LV mass was significantly influenced by intron 7 genotype ($P=0.009$), being modest among those of GG genotype (6.7±1.5 g), significantly greater in heterozygotes for the C allele (11.8±1.9 g), and 3-fold greater in CC homozygotes (19.4±4.2 g) (Figure 1A). These effects remained significant when LV mass was adjusted for body surface area ($P=0.02$) or lean mass

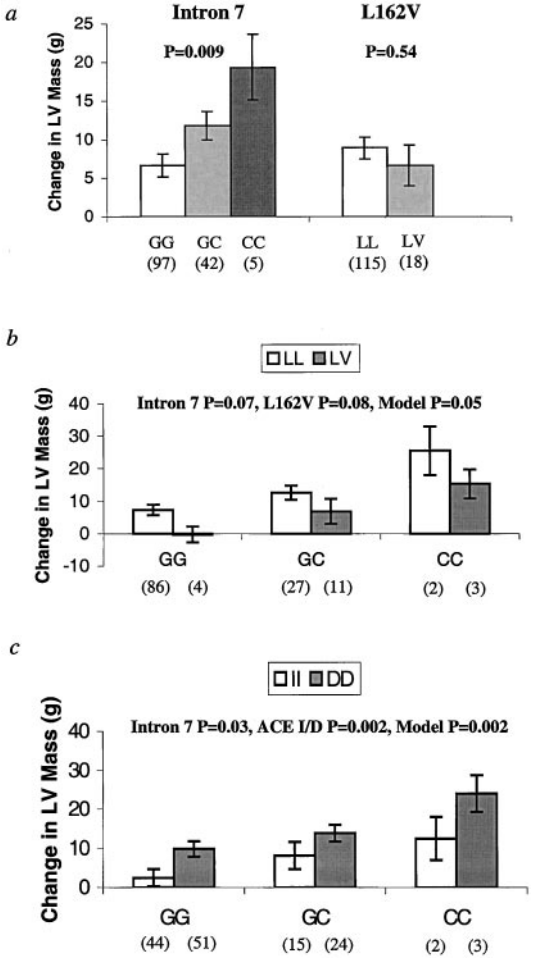

Figure 1. PPARα genotype influences increase in LV mass in response to exercise training. a, Intron 7 genotype influences cardiac growth response, and L162V genotype has no effect on cardiac growth. b, L162V genotype modifies effect of intron 7 genotype. L162 allele homozygotes are depicted as unfilled bars (LL); V162 allele carriers are depicted as filled bars (LV). c, ACE I/D genotype shows additive effects with PPARα intron 7 genotype. II allele homozygotes are depicted as unfilled bars (II); DD allele homozygotes are depicted as filled bars (DD). Numbers in each group are indicated in parentheses.

($P=0.03$), and there was no interaction between effect of genotype and losartan treatment. PPARα genotype did not significantly influence change in left and right ventricle volume measures (data not shown). PPARα L162V genotype alone did not influence change in LV mass (LeuLeu, 8.9±1.4 g; LeuVal, 6.7±2.7 g; $P=0.54$), but the V162 allele attenuated the hypertrophic effect of the intron 7 C allele when examined in combination with the intron 7 polymorphism (intron 7, $P=0.07$; L162V, $P=0.08$; combined, $P=0.05$) (Figure 1B). Given that participants were selected for homozygosity for the ACE gene I/D polymorphism,[22] we also examined for interaction between the ACE I/D and PPARα intron 7 genotypes. This analysis revealed that the ACE I/D and PPARα intron 7 genotypes had an independent effect on change in LV mass (ACE, $P=0.003$; PPARα, $P=0.026$). Subjects of II/GG genotype exhibited the lowest cardiac growth, whereas the individuals of DD/CC genotype exhibited the greatest exercise-related growth (Figure 1C). In a multiple regression model including all 3 genotypes determined, the effect on change in LV mass is calculated as +7.47±2.37 g for ACE DD, +5.06±2.80 g for carriers of the intron 7 C allele, +15.61±6.45g for intron 7 C allele homozygotes, and −6.2±3.74g for carriers of the V162 allele compared with ACE II, PPARα L162V LL, and intron 7 GG genotypes. Total variance in LV growth attributable to ACE I/D genotype was 8% ($P=0.002$), PPARα intron 7 genotype was 6% ($P=0.026$), and PPARα L162V genotype was 2.2% ($P=0.1$).

Effects in Response to Hypertension

To examine whether PPARα influences LV growth in response to pathophysiological stimuli, L162V and intron 7 genotype was determined in 578 men and 564 women participating in the echocardiographic substudy of the third MONICA Augsburg survey.[23] V162 allele frequency was 0.065 (95% CI, 0.055 to 0.075) and intron 7 C allele frequency was 0.179 (95% CI, 0.163 to 0.195), and the V162 and intron 7 C alleles showed significant allelic association. Both polymorphisms were in Hardy-Weinberg equilibrium.

There was no difference in age, BMI, or plasma lipid measures between L162V or intron 7 genotypes (data not shown). Systolic blood pressure was on average 6.8 mm Hg lower in male intron 7 C allele homozygotes than G allele homozygotes or C allele carriers ($P=0.13$) (Table 2). In multivariate regression analysis including age, antihypertensive medication, BMI, and systolic blood pressure, intron 7 genotype was significantly associated with left ventricular mass indexed to body surface area (LVMI) in men, with women showing a similar but nonsignificant trend. Male G allele homozygotes had an LVMI of 91.8±1.0, C allele carriers had an LVMI of 92.2±1.3 g/m^2, whereas C allele homozygotes had 15% greater mean LVMI of 105.7±4.8 g/m^2 ($P=0.005$). Female G allele homozygotes had an LVMI of 79.0±0.7 g/m^2, C allele carriers had an LVMI of 78.7±1.2 g/m^2, whereas C allele homozygotes had 7% higher LVMI of 84.6±3.8 g/m^2 ($P=0.14$). Similar effects were observed on septum and posterior wall measurements in men, and in women posterior wall diameter was significantly greater in C allele homozygotes than in homozygotes or carriers of the C allele, although septal wall thickness was similar between genotypes in women (Table 2). In the entire sample, with men and women combined, the hypertrophic effect of the CC genotype was highly significant for LVMI (CC 95.2±3.2 g/m^2 versus GG+GC 84.8±0.5 g/m^2, $P=0.001$), posterior wall (CC 9.43±0.21 mm versus GG+GC 8.66±0.03 mm, $P=0.0002$), and septum (CC 11.26±0.29 mm versus GG+GC 10.50±0.04 mm, $P=0.009$).

Interestingly, the effect of PPARα intron 7 genotype on LVMI was exacerbated in hypertensive individuals (n=319) (Figure 2). In normotensive individuals, C allele homozygotes had an LVMI of 87.3±3.2 g/m^2 ($P=0.04$ versus GG homozygotes) compared with 80.5±0.6 g/m^2 in G allele homozygotes and 81.2±0.9 g/m^2 in C allele carriers (overall effect of genotype, $P=0.07$) (Figure 2A). Hypertensive C allele homozygotes had a significantly greater LVMI of 114.6±7.0 g/m^2 compared with 99.0±1.5 g/m^2 for G allele

TABLE 2. LV Mass and Blood Pressure Measurements in the Third MONICA Augsburg Study by PPARα Intron 7 Genotype

	Men				Women			
	GG (n=372)	GC (n=191)	CC (n=15)	*P*	GG (n=396)	GC (n=161)	CC (n=15)	*P*
LVMI, g/m^2	91.8±1.0	92.2±1.3	105.7±4.8	0.005	79.0±0.7	78.7±1.2	84.6±3.8	0.144
Septal wall, mm	11.1±0.08	11.2±0.11	12.3±0.43	0.009	10.1±0.07	10.1±0.11	10.3±0.38	0.387
Posterior wall, mm	9.2±0.05	9.2±0.08	9.9±0.30	0.011	8.3±0.06	8.4±0.09	8.9±0.29	0.009
LVEDD, mm	50.1±0.22	50.1±0.31	50.4±1.16	0.870	45.8±0.19	45.7±0.31	45.7±1.02	0.830
LVH, %	5.4	4.2	20.0	0.033	9.6	9.0	13.3	0.890
SBP, mm Hg	135.8±0.89	138.1±1.23	129.8±4.43	0.13	130.8±0.83	130.7±1.29	129.5±4.25	0.77
DBP, mm Hg	82.4±0.58	84.3±0.82	79.6±2.92	0.25	78.6±0.53	78.5±0.83	80.1±2.75	0.60

Values are least square means±SE, adjusted for age, BMI, systolic blood pressure, and antihypertensive medication (SBP and DBP not adjusted for systolic blood pressure).

LVEDD indicates left ventricular end-diastolic dimension; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

P values are for combined GG and GC genotypes compared with CC genotype.

homozygotes (P=0.03 CC versus GG) and 97.7±2.2 g/m^2 in C allele carriers (P=0.02) (Figure 2B). Male C allele homozygotes were 4 times more likely to have clinically defined LVH than G allele homozygotes or C allele carriers (0.20 versus 0.05, P=0.03), an effect not observed in females (0.13 versus 0.10, P=0.89) (Figure 3). L162V genotype had no effect on LV measures (data not shown). No effect was observed on left ventricle end-diastolic dimensions, left atrial diameter, and aortic root diameter for either PPARα genotype (data not shown).

Discussion

PPARα plays a key role in the regulation of cardiac FA uptake and oxidation and may be the mediator, at least in part, of the metabolic switch from FA to glucose during hypertrophy. It is conceivable that PPARα could influence cardiac growth through the modulation of cardiac FAO. The data presented support this notion, because they demonstrate that common variation in the PPARα gene influences human LV growth in response to exercise and hypertension, 2 distinct stimuli that influence LVH. There is a growing body of evidence that appropriate substrate use is critical for cardiac function. Defects in FAO enzymes cause childhood cardiomyopathies,[9] and pharmacological inhibition of cardiac FA import induces cardiac hypertrophy[26] and causes rapid death in PPARα-knockout mice.[20] Transgenic mice that overexpress long-chain acyl-CoA synthetase and take up excess long chain fatty acids initially exhibit cardiac hypertrophy, followed by LV dysfunction and death.[11] These data clearly show that appropriate regulation of cardiac substrate use is essential for normal cardiac function.

Exercise-induced LV growth in healthy young men was strongly influenced by the intron 7 polymorphism of the PPARα gene, an effect modulated by the L162V polymorphism. Individuals homozygous for the C allele had a 3-fold greater and heterozygotes had a 2-fold greater increase in LV mass than G allele homozygotes. The additive effect of the PPARα intron 7 and ACE I/D polymorphisms indicates that these hypertrophic pathways act independently. Thus, PPARα is a regulator of LV growth in response to an intense short-term physiological stimulus.

The PPARα intron 7 polymorphism was also associated with left ventricular mass and the presence of clinically defined LVH in a population-based sample of the third MONICA Augsburg survey. The effect on left ventricular mass was much stronger in men, although women showed a similar nonsignificant trend, and was significant in the whole population when men and women were combined. The hypertrophic effect of the intron 7 C allele was ≈2-fold greater in hypertensive than normotensive subjects, indicating that PPARα influences the degree of LV growth in response to hypertension but also influences growth in the absence of an obvious stimulus. The hypertrophic effect of the intron 7 C allele is not mediated through raised systolic blood pressure, because intron 7 C allele homozygotes have lower systolic blood pressure than G allele homozygotes or C allele carriers. In contrast to exercise-induced hypertrophy, in which an

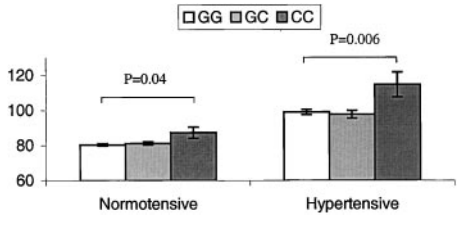

Figure 2. Effect of PPARα intron 7 genotype on LVMI in normotensive and hypertensive individuals.

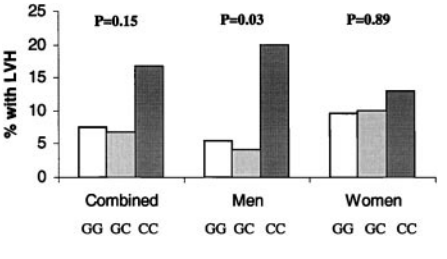

Figure 3. PPARα intron 7 genotype increases risk of clinically defined LVH.

intermediate effect on change in LV mass was observed in GC heterozygotes, the hypertrophic effect of the intron 7 polymorphism was restricted to C allele homozygotes, with heterozygotes having virtually identical LV measures to G allele homozygotes. The L162V polymorphism did not influence LV measures in the Third MONICA Augsburg study. We hypothesize that these differences are attributable to the contrasting nature of a strong short-term exercise stimulus and the low-level long-term stimulus of hypertension. These data clearly demonstrate that PPARα plays an important role in the regulation of LV growth in response to both exercise and blood pressure stimuli, thus identifying a novel pathway for the regulation of cardiac growth. The genetic contribution to total variance in LV mass is estimated at >60% in early pubertal children,[5] whereas heritability of LV mass was estimated at 0.24 to 0.32 in adults in the Framingham Study.[27] In the army study, PPARα intron 7 and L162V genotypes explained 6% and 2.2% of total variance in change in LV mass in the study, whereas the ACE I/D genotype was responsible for an additional 8% of variance.

The sexually dimorphic effect on cardiac growth of PPARα polymorphisms parallels effects observed in PPARα-knockout mice. Male PPARα-knockout mice treated with etomoxir, an inhibitor of mitochondrial LCFA import, show massive hepatic and cardiac lipid accumulation and hypoglycemia, and all die after 4 days of treatment, whereas mortality is only 25% in females. The female mice that died also had severe hypoglycemia, and male mice exhibiting lethargy recovered on dextrose injection, indicating that severe hypoglycemia may be directly responsible for death. Male mice pretreated with estradiol were protected from the ill effects of etomoxir.[20] Aging male PPARα-knockout mice also exhibit hepatic steatohepatitis, whereas females show late-onset obesity and hypertriglyceridemia.[28]

The mechanism by which the intron 7 polymorphism affects PPARα function remains unclear. The intron 7 C allele is in allelic association with the V162 allele, which encodes a more transcriptionally active PPARα[21] and attenuates the effect of the intron 7 C allele on exercise-induced LVH. We speculate that the intron 7 polymorphism is in allelic association with an unidentified variant in a regulatory region of the PPARα gene that affects PPARα levels, which in turn affect transcriptional activation of PPARα target genes. Efforts to examine the effect of intron 7 genotype on PPARα mRNA levels and to identify functional promoter variants are presently underway.

In summary, these data constitute strong evidence that PPARα regulates left ventricular growth in response to exercise and hypertension stimuli and illustrate the important role of cardiac fatty acid metabolism in cardiac growth. These data may have therapeutic implications for patients with LVH. Stimulation of FAO by PPARα activation with fibrates may prove a useful therapeutic strategy for treatment of a subset of patients with LVH.

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