Human skeletal muscle PPARα expression correlates with fat metabolism gene expression but not BMI or insulin sensitivity

Junlong Zhang,1 D. I. W. Phillips,2 Chunli Wang,1 and Christopher D. Byrne1

1Endocrinology and Metabolism Unit, Fetal Origins of Adult Disease Division, School of Medicine, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, and 2Medical Research Council Environmental Epidemiology Unit, Southampton General Hospital, Southampton SO16 5YD, United Kingdom

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Zhang, Junlong, D. I. W. Phillips, Chunli Wang, and Christopher D. Byrne. Human skeletal muscle PPARα expression correlates with fat metabolism gene expression but not BMI or insulin sensitivity. Am J Physiol Endocrinol Metab 286: E168–E175, 2004.—Peroxisomal proliferator-activated receptor-α (PPARα) is a transcription factor that belongs to a family of transcription factors that form heterodimers with retinoid X receptors. PPARs also include PPARγ and -β (34), and fatty acids or their metabolites are probably their natural ligands (34). PPARα regulates fatty acid oxidation (33) and is well expressed in tissues active in lipid metabolism, including liver, skeletal muscle, and adipose and kidney tissues (34). For example, expression of muscle carnitine palmitoyltransferase-I (mCPT-I), a rate-limiting enzyme in skeletal muscle fatty acid oxidation (22), is regulated by PPARα in vitro (21). Expression of CD36, an important transporter of long-chain fatty acid, is regulated by PPARα (26, 31) and γ in the liver (24). Expression of lipoprotein lipase (LPL) is regulated by PPARα in the liver (26, 32) and PPARγ in adipocytes (32). LPL hydrolyses lipoprotein triglyceride (TG) to free fatty acid and monoglycerides, permitting their uptake into muscle for oxidation (11). Therefore, activity of PPARα plays a key role in regulating expression of key genes in lipid metabolism, but much of the data to date have been obtained in animal models and the relationships have not been defined for individual insulin-sensitive tissues and are therefore not fully understood in humans in vivo.

PPARα activity can be affected by PPARα mRNA levels. For example, in PPARα transgenic overexpressing mice, PPARα protein level is increased (10). mRNA levels of PPARα response genes (e.g., acyl-CoA oxidase and CPT-I), and CPT-I activity are also increased in overexpressing PPARα transgenic mice (10). Importantly, the magnitude of increase in mRNA levels of the PPARα response gene (e.g., acyl-CoA oxidase) and in CPT-I activity is markedly greater in PPARα transgenic mice than those from nontransgenic controls (10), whereas in PPARα knockout mice mRNA and protein levels from PPARα response genes (e.g., long-chain and very long-chain acyl-CoA dehydrogenase; see Ref. 1) are all reduced. Therefore, useful information on PPARα activity can be obtained by measuring changes in PPARα mRNA levels.

In fasting conditions, lipid oxidation is the predominant metabolic activity of skeletal muscle (6), and the majority of the energy requirement of skeletal muscle is obtained from fatty acid oxidation (6). The aim of this study was to investigate in humans in vivo the relationship between insulin sensitivity and body mass index (BMI), with fasting PPARα expression in skeletal muscle. We measured PPARα mRNA...
 levels and mRNA levels of known PPARα response genes, because for many years inhibition of glucose metabolism by fat metabolism has been proposed as a factor responsible for reducing insulin sensitivity (28).

MATERIALS AND METHODS

Subjects. Out of 36 subjects recruited, 16 adult men not known to have diabetes agreed to undergo skeletal muscle biopsy for this study (Table 1). On investigation, 14 subjects had normal glucose tolerance, whereas 2 subjects had glucose levels compatible with (undiagnosed) diabetes mellitus by World Health Organization criteria. No subjects had fasting glucose levels and mRNA levels of known PPARα response genes, because for many years inhibition of glucose metabolism by fat metabolism has been proposed as a factor responsible for reducing insulin sensitivity (28).

Table 2. List of PCR primers and sizes of amplified PCR products

<table>
<thead>
<tr>
<th>Genes</th>
<th>Sequences (5'-3')</th>
<th>Sizes of PCR Products</th>
<th>Access No.</th>
</tr>
</thead>
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<tr>
<td>18S rRNA</td>
<td>Sense: GGGCTGTAATTGGAGTACGTC  &lt;br&gt;Antisense: TCAGCCGAGCTGTCCTGTG</td>
<td>450</td>
<td>M10098</td>
</tr>
<tr>
<td>mCPT-1</td>
<td>Sense: CTCACTATTGACTGCTGCA  &lt;br&gt;Antisense: GGTCCTTTAGTCATCTGTC</td>
<td>441</td>
<td>M58581</td>
</tr>
<tr>
<td>CD36</td>
<td>Sense: CCAAGACAATTGATTGTCTGC  &lt;br&gt;Antisense: TCCTTTCTGAGTTTCTTG</td>
<td>446</td>
<td>L06850</td>
</tr>
<tr>
<td>GLUT4</td>
<td>Sense: AGAGATTTGAGGATCTTGG  &lt;br&gt;Antisense: AATCTTTGAGGATCTTGG</td>
<td>446</td>
<td>M20747</td>
</tr>
<tr>
<td>LPL</td>
<td>Sense: TGTTGGGACTGATCCCTGAG  &lt;br&gt;Antisense: CTGTTGGGACTGATCCCTGAG</td>
<td>446</td>
<td>X54516</td>
</tr>
<tr>
<td>PPARα</td>
<td>Sense: GGTACCTGAGTGCTGG  &lt;br&gt;Antisense: CAGAGCTGAGTGCTGG</td>
<td>442</td>
<td>S74349</td>
</tr>
<tr>
<td>UCP-2</td>
<td>Sense: TCAGCAGCTGAGTGCTGG  &lt;br&gt;Antisense: TGGCTGAGCTGAGTGCTGG</td>
<td>443</td>
<td>NM_003355</td>
</tr>
<tr>
<td>UCP-3</td>
<td>Sense: TGGAGCTGAGCTGAGTGCTGG  &lt;br&gt;Antisense: GGTACCTGAGCTGAGTGCTGG</td>
<td>444</td>
<td>XM_006360</td>
</tr>
</tbody>
</table>

mCPT-1, muscle-type carnitine palmitoyltransferase-1; GLUT, glucose transporter; LPL, lipoprotein lipase; PPARα, peroxisome proliferator-activated receptor-α; UCP-2 and -3, uncoupling proteins-2 and -3.

Fig. 1. Multiplex standard DNA. The multiplex standard DNA fragment contains 11 genes. Data from 7 genes are presented and shown. The sequences of primers for the 7 genes are presented in Table 2. The size for PCR products of each of these genes is similar. CPT, carnitine palmitoyltransferase; LPL, lipoprotein lipase; PPARα, peroxisome proliferator-activated receptor; UCP, uncoupling protein; GRα, glucocorticoid receptor-α; M.GS, muscle glycogen synthase; IR, insulin receptor; GHR, growth hormone receptor.
was cloned into a pGEM-T easy vector (Promega, Southampton, UK) in Escherichia coli JM 109 strain according to the manufacturer's protocol. Colonies harboring msDNA were identified. msDNA fragment was excised from plasmids (MH01), prepared from a single colony grown overnight, by digesting with EcoRI enzyme (Fig. 1). msDNA fragment was gel purified, dissolved in H2O, and quantified by spectrophotometry.

**Total RNA preparation.** Total RNA was prepared as described previously ([5](#)) from frozen tissue biopsies. About 30 mg of skeletal muscle were placed in 400 μl of solution containing 4 M guanidinium thiocyanate, 25 mM sodium citrate (pH 7), 0.5% sarcosyl, and 0.1 M 2-mercaptoethanol in a 1.5-ml Eppendorf tube on ice. The tissue was homogenized, and 40 μl of 2 M sodium acetate (pH 4.0) were added and mixed to precipitate genenomic DNA. The protein and lipids in the preparation were extracted by adding 400 μl phenol (pH 4.3, saturated with 0.1 M citrate buffer) and 100 μl chloroform-isomyl alcohol (49:1 vol/vol); they were then mixed well and left in ice for 5–10 min. The samples were centrifuged at 12,000 g for 15 min to separate the aqueous phase with phenol phase. The upper aqueous phase was carefully transferred to a fresh 1.5-ml Eppendorf tube. The extraction with phenol and chloroform-isomyl alcohol (49:1 vol/vol) was repeated one or two times, until no protein was visible in the layer between the aqueous and phenol phase. After the upper aqueous phase was transferred to a fresh 1.5-ml Eppendorf tube, three volumes of absolute ethanol were added, and the samples were left on dry ice or at −70°C for 20 min to precipitate the RNA. The precipitated RNA was collected by centrifugation at 12,000 g at 4°C for 20 min. The ethanol was discarded, and the pellet was washed with 0.5 ml of 70% ethanol one time. The 70% ethanol was carefully discarded after centrifugation at 12,000 g at room temperature for 5 min. The pellet was dried at 37°C for 10–15 min and dissolved in ~30 μl diethyl pyrocarbonate-treated H2O. The yield of total RNA was measured by spectrophotometry.

**cDNA synthesis.** Total RNA (5 μg) in 50 μl of RNase-free H2O was denatured at 70°C for 5 min and then chilled to 4°C. Denatured total RNA was added with 0.5 mM dNTP mix, 5 μM random hexamers, 10 U/μl Moloney murine leukemia virus (MMLV) RT (Promega), and 1 U/μl RNasin (Promega) in 1× MMLV RT buffer [Promega, containing 50 mM Tris-HCl (pH 8.3 at 25°C), 75 mM KCl, 5 mM MgCl2, and 10 mM DTT] and H2O to make a final volume of 100 μl. The cDNA reaction was incubated for 1 h at 42°C and stopped by heating at 95°C for 5 min.

**mRNA quantification from multiple genes.** mRNA levels were quantified using a medium-throughput quantitative competitive PCR (MT-qPCR) developed in our laboratory that can detect an ~15% difference in mRNA levels ([35](#)). Briefly, cDNA (containing ~25 ng total RNA), msDNA (e.g., 0.17 pm for PCR amplification by 27 cycles, 0.084 pm for 28 cycles, etc; the msDNA concentrations were reduced by 1.9-fold as the number of PCR amplification cycles increased by 1), 0.4 μM gene-specific PCR primers for one gene, and 1× PCR Ready-Mix (containing 0.3 units Taq polymerase, 10 mM Tris-Cl, 50 mM KCl, 1.5 mM MgCl2, 0.001% gelatin, 0.2 mM dNTP, and stabilizers) in a total of 10 μl reaction volume were added to each well in a 96-well plate. Reactions in the 96-well plate were amplified by a given PCR cycle number under the following conditions: 4 min of preliminary heating at 94°C followed by 50 s denaturation at 94°C, 50 s annealing at 57°C and 1-min extension at 72°C, and a final 5-min extension at 72°C. For each gene analyzed, data were obtained from PCR reactions with 4 different cycle numbers, i.e., for simultaneous analysis of mRNA levels from 8 genes × 11 samples, 4 different PCR plates were amplified by 27, 28, 29, or 30 cycles, respectively. The PCR reaction conditions between these plates were identical except that the concentrations of msDNA were reduced sequentially by 1.9-fold in relation to increasing PCR cycle numbers (Fig. 2). Mean values of mRNA levels for each single gene were calculated from mRNA levels obtained from four different cycle numbers. The assay was repeated one time to verify the reproducibility of data. Amplified PCR products from different genes were confirmed by sequencing.

**Data analysis.** Five microliters of each PCR product (up to 96 samples) were analyzed with a microplate diagonal gel electrophoresis containing 5% polyacrylamide, as described previously ([35](#)), stained in ethidium bromide, and destained in H2O for 30 min. The picture was taken with a digital camera (UVF, Cambridge, UK), and the image of the gel was saved on a floppy disk. The fluorescence of DNA bands was analyzed using Phoretix 1 D advanced v. 4.01 (Newcastle upon Tyne, UK) software. The detailed procedure for data analysis was described previously ([35](#)). mRNA levels were calculated and presented as arbitrary units. Values of mRNA levels from target genes were normalized to mRNA levels of 18S rRNA, measured with quantitative competitive PCR using a synthetic standard DNA for 18S rRNA.

**Statistical analysis.** Pearson correlation analysis was performed using SPSS software (version 10.1.0). Correlation is significant at a P value < 0.05.

**RESULTS.** Subjects were recruited from the local community with a wide variation in BMI (23.6–39 kg/m2) to allow us to examine relationships between BMI, insulin sensitivity, and PPARα expression. Values of BMI were negatively correlated with the insulin sensitivity index (r = −0.73, P = 0.001, n = 16). The insulin sensitivity index values (ratio of metabolized glucose to mean plasma insulin), as a measure of whole body insulin-mediated glucose disposal, ranged between 2.6 and 10.1 (mg−m2−min−1μU−1ml−1) in this cohort (Table 1).

To determine whether steady-state PPARα mRNA levels correlate with mRNA levels of genes regulating fat metabolism, mRNA levels from PPARα and key genes in lipid metabolism were measured in skeletal muscle biopsies obtained after overnight fasting, before hyperinsulinemic-euglycemic clamp study, using MT qPCR (Fig. 2). A strong, significant and positive correlation was observed between mRNA levels of PPARα and CD36 (r = 0.77, P = 0.001, n = 14; Fig. 3A), PPARα and LPL (r = 0.54, P = 0.024; Fig. 3B), PPARα and uncoupling protein (UCP)-3 (r = 0.53, P = 0.026; Fig. 3C), PPARα and UCP-2 (r = 0.63, P = 0.008; Fig. 3E), and PPARα and mCPT-I (r = 0.54, P = 0.024; Fig. 3D). In contrast, the association between mRNA levels of PPARα and GLUT4 was not significant (r = 0.38, P = 0.09, Fig. 4A), and no association was observed between mRNA levels of PPARα and insulin sensitivity index values (r = −0.04, P = 0.44, Fig. 4B) or BMI (r = 0.3, P = 0.15, Fig. 4C).

Because the study recruited subjects with a wide range of BMI (23–39 kg/m2), we also analyzed data by stratifying nonobese subjects (BMI <30 kg/m2) and obese subjects (BMI >30 kg/m2, Table 3). PPARα strongly correlated with CD36 (r = 0.99, P < 0.001) and LPL (r = 0.80, P = 0.01) in nonobese subjects (Table 3). There was a trend toward a weaker correlation in subjects with increasing BMI (r = 0.68, P = 0.07 for CD36 and r = 0.36, P = 0.28 for LPL). PPARα correlated well with mCPT-I in all subjects. Interestingly, there was a trend toward a stronger correlation in obese subjects (r = 0.98, P = 0.01, Table 3). PPARα correlated with UCP-3 (r = 0.74, P = 0.02) and GLUT4 (r = 0.64, P = 0.05) mainly in nonobese subjects, and the significant correlation was not present in obese subjects. There was no correlation between PPARα and BMI or insulin sensitivity index values in either group.
DISCUSSION

Existing data show that there is a differential response to PPARα between humans and rodents (19). For example, acyl-CoA oxidase, a PPARα response gene in liver in rodents, is not responsive to PPARα in human liver (19, 30); a similar phenomenon exists with peroxisomal enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase (19). Thus data obtained from rodents may not be directly applied to humans; therefore, it is important to obtain data in humans in vivo.

Here we show that expression of mRNA levels of PPARα is closely correlated with mRNA levels of CD36, LPL, UCP-2, UCP-3, and mCPT-I (Fig. 5) but not with a key gene in glucose metabolism such as GLUT4 nor BMI or insulin sensitivity index. Importantly, correlations were not observed between PPARα and the housekeeping gene 18S rRNA. The novelty of this study is that (1) expression of PPARα and genes controlling fat metabolism are tightly linked in human skeletal muscle in vivo; (2) no relationships are observed between PPARα expression in skeletal muscle tissue and insulin sensitivity, as measured by the hyperinsulinemic-euglycemic clamp; 3) no relationships occur between PPARα expression in skeletal muscle tissue and BMI as a measure of obesity; and 4) our novel mRNA methodology (35) has made this study possible in limited human biopsy material.

The mechanism underlying activation of PPARα and improved insulin sensitivity is not fully understood. In animal studies, administration of PPARα agonist reduces body insulin resistance induced by high-fat feeding (13) or high-fructose feeding (27). In human studies, administration of PPARα agonist also improves insulin sensitivity and lipid profile (15).

The underlying mechanisms may be explained by 1) activation of PPARα, redirecting fatty acids from peripheral tissues (e.g., skeletal muscle) to the liver, because hepatic PPARα CPT-I and CD36 expression is increased (13) by PPARα agonist administration; and/or 2) increased glucose utilization in adipose tissue because GLUT4 mRNA levels are increased in visceral adipose tissue by lipid infusion (7). Thus activation of PPARα in other tissues such as liver might reduce the fatty acid-mediated inhibition of insulin-stimulated glucose disposal in skeletal muscle (2, 13). These data and our results suggest
that it is unlikely that activation of PPARα directly increases glucose utilization in skeletal muscle although skeletal muscle plays a major role in whole body glucose utilization.

Our data show that PPARα mRNA levels in skeletal muscle do not correlate with body insulin sensitivity (Fig. 4B, in particular, in obese subjects, Table 3), i.e., there was no marked difference in PPARα mRNA levels in subjects with different insulin sensitivity indexes (Fig. 4B). Our data seem therefore to be also consistent with an earlier report showing that skeletal muscle PPARα protein levels were similar between nondiabetic and diabetic subjects (20). We consider that these data do not contradict the concept that activation of PPARα improves insulin sensitivity, as discussed above. In our nonobese subjects, for example, PPARα positively correlates with GLUT4 mRNA levels ($r = 0.64, P = 0.05$, Table 3), and a similar trend is also shown between PPARα and the insulin sensitivity index ($r = 0.52, P = 0.09$, Table 3). These relationships were weaker in obese subjects (Table 3). Thus the evidence suggests that increased fatty acid metabolism in skeletal muscle does not increase skeletal muscle glucose metabolism. The mechanism probably involves increased fatty acid metabolism, antagonizing insulin-induced glucose utilization and oxidation (28). This notion is consistent with an earlier report in humans showing that a lipid-heparin infusion reduces glucose uptake (9) and in animal studies that lipid-heparin infusion increases skeletal muscle CD36 mRNA levels but reduces skeletal muscle GLUT4 mRNA levels and skeletal muscle glucose utilization (7).

CD36 is a key transporter for lipid uptake in skeletal muscle (3) and LPL hydrolyzes TG to release fatty acids for oxidation. Expression of CD36 and LPL is mainly regulated by PPARα in liver (26, 31) and by PPARγ in adipocytes (26, 31). To date, it has been uncertain whether expression of CD36 or LPL is regulated by PPARα or -γ in human skeletal muscle in vivo.
Although both PPAR\(\alpha\)/H9251 (20) and PPAR\(\gamma\)/H9253 are expressed (8, 20), the levels of PPAR\(\gamma\)/H9253 mRNA are barely detectable in our experiments (data not shown), consistent with a previous report (8). Our data showing a positive and significant correlation between mRNA levels of PPAR\(\alpha\)/H9251 and those of CD36 or LPL suggest that PPAR\(\alpha\)/H9251 may be an important regulator of CD36 and LPL in vivo in humans in skeletal muscle, although such a correlation is not a direct proof that PPAR\(\alpha\)/H9251 is a regulator of CD36 and LPL in humans in vivo.

mCPT-I plays a key role in mitochondrial fatty acid oxidation. Administration of PPAR\(\alpha\) agonists upregulates muscle CPT-I in hamster and stimulates fatty acid \(\beta\)-oxidation in human skeletal muscle cells (25). Human mCPT-I is stimulated by fatty acids, a response that is thought to be mediated by a peroxisome proliferator response element to which PPAR\(\alpha\) binds (21). Interestingly, PPAR\(\gamma\) mRNA also correlates with mRNA levels of mCPT-I and LPL in human skeletal muscle (18). Thus it is possible that activation of either PPAR\(\alpha\) or PPAR\(\gamma\) might affect expression of mCPT-I.

Interestingly, there is a suggestion (albeit the numbers are small) that the correlation between PPAR\(\alpha\) and mCPT-I is stronger in obese subjects than in nonobese subjects in our study (Table 3). These data suggest that, in obese subjects, fatty acid oxidation in skeletal muscle might also be increased, probably because of increased circulating concentrations of free fatty acids often seen in obesity (12).

UCP-2 and UCP-3 are proteins that uncouple substrate oxidation from ATP synthesis, converting fuel into heat energy (17). Whether expression of UCPs is regulated in humans by PPARs in vivo has not been determined. PPAR\(\alpha\) agonists upregulate expression of UCP-3 in rat skeletal muscle (4). Our data showing a positive correlation between PPAR\(\alpha\) and UCP-2 and UCP-3 suggest that, in human skeletal muscle in vivo, PPAR\(\alpha\) regulates expression of UCP-2 and UCP-3.

### Table 3. Correlations between mRNA levels of PPAR\(\alpha\) and mRNA levels of genes in lipid metabolism and BMI or M-to-I ratios stratified by BMI

<table>
<thead>
<tr>
<th>Genes</th>
<th>BMI &lt;30 kg/m(^2)</th>
<th>BMI &gt;30 kg/m(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPAR(\alpha) vs. CD36</td>
<td>0.99 0.000 8</td>
<td>0.68 0.07 6</td>
</tr>
<tr>
<td>PPAR(\alpha) vs. LPL</td>
<td>0.80 0.01 8</td>
<td>0.36 0.28 5</td>
</tr>
<tr>
<td>PPAR(\alpha) vs. CPT-I</td>
<td>0.75 0.03 7</td>
<td>0.98 0.01 4</td>
</tr>
<tr>
<td>PPAR(\alpha) vs. UCP-2</td>
<td>0.55 0.08 8</td>
<td>0.66 0.08 6</td>
</tr>
<tr>
<td>PPAR(\alpha) vs. UCP-3</td>
<td>0.74 0.02 8</td>
<td>0.47 0.17 6</td>
</tr>
<tr>
<td>PPAR(\alpha) vs. GLUT4</td>
<td>0.64 0.05 8</td>
<td>0.31 0.27 6</td>
</tr>
<tr>
<td>PPAR(\alpha) vs. BMI</td>
<td>-0.13 0.38 8</td>
<td>0.27 0.30 6</td>
</tr>
<tr>
<td>PPAR(\alpha) vs. M-to-I ratios</td>
<td>0.52 0.09 8</td>
<td>-0.04 0.46 6</td>
</tr>
</tbody>
</table>

\(N\), no. of subjects.

Fig. 4. Correlation between mRNA levels (AU) of PPAR\(\alpha\) with mRNA levels of GLUT4 (A), insulin sensitivity index (ratio of the amount of glucose metabolized to the mean plasma insulin during steady state; B), and body mass index (BMI; C). Each point represents the mean value of 2 determinations (for each determination, mean values were taken from 4 different PCR cycles).

Fig. 5. Correlation between mRNA levels of PPAR\(\alpha\) and mRNA levels of important genes in lipid metabolism. No correlation between mRNA levels of PPAR\(\alpha\) and mRNA levels of GLUT4 (\(r = 0.38, P = 0.09\)), BMI (\(r = 0.3, P = 0.15\)), and insulin sensitivity index (\(r = -0.04, P = 0.44\)) was observed. The 2-headed arrows between PPAR\(\alpha\) and each gene represent that expression of PPAR\(\alpha\) correlated with expression of those genes.
Insulin sensitivity measured by the hyperinsulinemic-euglycemic clamp represents insulin-mediated whole body glucose disposal, and insulin sensitivity is affected by tissue insulin sensitivity, mainly in liver, skeletal muscle, and adipose tissues. Our data do not show any correlation between PPARα mRNA levels in skeletal muscle with hyperinsulinemic-euglycemic clamp, mainly in liver, skeletal muscle, and adipose tissue. The insulin-mediated whole body glucose disposal is not affected by PPARα mRNA levels, since the majority of insulin-induced glucose uptake during the clamp occurs in skeletal muscle.

It would have been ideal if we could have taken a second biopsy from these volunteers after the clamp study to investigate changes in gene expression. However, it was neither practical nor ethical in unpaid volunteers to do so given the painful procedure these volunteers had to experience. Only 16 of our original 36 recruited subjects agreed to undergo muscle biopsy. Because the amount of tissue biopsy obtained was very small (the smallest amount was ~26 mg), we were unable to analyze protein expression.

In summary, we have shown for the first time in humans in vivo, using unique mRNA measurement methodology for a range of relevant genes, that mRNA levels of PPARα strongly correlate with mRNA levels of several key genes regulating fat metabolism in skeletal muscle. A measure of insulin sensitivity and BMI did not correlate with PPARα expression in skeletal muscle tissue. Although not proof of causality, these novel results suggest that, in humans in vivo, PPARα expression plays an important role in coordinate regulation of key genes in lipid but not glucose metabolism.

GRANTS

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REFERENCES


