Overexpression of Peroxisome Proliferator-activated Receptor γ Coactivator-1α Down-regulates GLUT4 mRNA in Skeletal Muscles*

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Exercise training increases mitochondria and GLUT4 in skeletal muscles. Recent studies indicate that an increased expression of the transcriptional coactivator peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) by exercise may promote mitochondrial biogenesis and fatty acid oxidation. To examine whether increased PGC-1α expression was also responsible for an increase of GLUT4 expression, transgenic mice that overexpress PGC-1α in skeletal muscles driven by a human α-skeletal actin promoter were made. PGC-1α was overexpressed in skeletal muscles including type I and II fiber-rich muscles but not in the heart. With an increase of PGC-1α mRNA, type II fiber-rich muscles were redder, and genes of mitochondrial oxidative metabolism were up-regulated in skeletal muscles, whereas the expression of GLUT4 mRNA was unexpectedly down-regulated. In parallel with a decrease of GLUT4 mRNA, an impairment of glycemic control after intraperitoneal insulin administration was observed. Thus, an increase of PGC-1α plays a role in increasing mitochondrial biogenesis and fatty acid oxidation but not in increasing GLUT4 mRNA in skeletal muscles.

Endurance exercise training improves physical performance by an enhancement of skeletal muscle respiratory capacity (1) and decreases the incidence rate of diabetes mellitus (2). These effects might be related to increased numbers of mitochondria and the GLUT4 isoform of the glucose transporter in skeletal muscles, respectively. GLUT4, the insulin-responsive glucose transporter, is expressed in skeletal muscles, heart, and adipose tissues, and the number of GLUT4 on plasma membrane becomes a rate-limiting step for whole-body glucose clearance under physiological conditions (3–5). Thus, exercise training modifies the skeletal muscle to metabolize more fatty acids and glucose.

As for mitochondrial biogenesis, two transcription factors, nuclear respiratory factor (NRF)-1 and NRF-2, were key transcriptional activators of nuclear genes encoding mitochondrial enzymes (6, 7). NRFs up-regulate mitochondrial transcription factor A, which stimulates mitochondrial DNA transcription and replication (8). Recently, as a regulator of NRFs, peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1α) was found. PGC-1α is an inducible coactivator of nuclear receptors cloned from brown fat cell cDNA library because of its interaction with peroxisome proliferator-activated receptor γ (PPARγ) (9). Overexpression of PGC-1α increased expression of mitochondrial enzymes in 3T3 adipocytes, stimulated mitochondrial biogenesis in C2C12 myocytes (9, 10), and induced the expression of nuclear and mitochondrial genes involved in multiple mitochondrial energy production pathways, including PPARα target genes encoding the mitochondrial fatty acid β-oxidation in neonatal cardiac myocytes (11). In vivo cardiac-specific overexpression of PGC-1α in transgenic mice resulted in uncontrolled massive proliferation of mitochondria (11). Also, evidence that PGC-1α co-activated PPARαs (12) and NRF-1 (10) led to a new hypothesis that PGC-1α is a key molecule for the entire fatty acid oxidation system, including intracellular fatty acid transport, fatty acid β-oxidation, tricarboxylic acid cycle, and respiratory chain.

In contrast, although nucleotide sequences of GLUT4 promoter responsible for exercise training-induced up-regulation of GLUT4 expression have been elucidated (13, 14), little is known about the transcription factor(s) by which exercise training stimulates GLUT4 expression (15). Because overexpression of PGC-1α in type II (fast-twitch) fibers drives the formation of type I (slow-twitch) fibers (16) and type I fibers express more GLUT4 with an increased glucose uptake than type II fibers (17), PGC-1α may also up-regulate GLUT4 expression in skeletal muscles directly and indirectly. Indeed, adenovirus-mediated expression of PGC-1α in cultured muscle cell lines L6 myotube resulted in a large increase in GLUT4, providing evidence that PGC-1α can also up-regulate GLUT4 gene expression (18). However, there has been some evidence against this hypothesis. Starvation increased the capacity for mitochondrial energy production via fatty acid β-oxidation with a marked up-regulation of PGC-1α in the heart (11), whereas starvation did not increase GLUT4 in skeletal muscles (19). A single bout of exercise increased PGC-1α mRNA and protein (20), but did not increase GLUT4 mRNA (21). A significant GLUT4 expression was observed by prolonged exercise or repeated bouts of exercise (21). To resolve this question, we made mice that overexpressed PGC-1α in skeletal muscle and examined whether PGC-1α increases GLUT4 expression as well as enzymes related to mitochondrial biogenesis and fatty acid oxidation.

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1 The abbreviations used are: NRF, nuclear respiratory factor; PGC-1α, peroxisome proliferator-activated receptor γ coactivator; PPAR, peroxisome proliferator-activated receptor; MEF2C, myocyte specific enhancer factor 2C; COX, cytochrome c oxidase; MCAD, medium-chain acyl-CoA dehydrogenase; LPL, lipoprotein lipase; ACO, acyl-CoA oxidase; TA, tibialis anterior; EDL, extensor digitorum longus.

Received for publication, April 24, 2003
Published, JBC Papers in Press, May 29, 2003, DOI 10.1074/jbc.M304312200

* This work was supported in part by a grant-in-aid for Scientific Research Kakenhi 14770030 (to S.M.) from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Tokyo), by research grants from the Japanese Ministry of Health, Labor and Welfare (Tokyo), and by a Grant from the Promotion of Fundamental Studies in Health Sciences of Organization for Pharmaceutical Safety and Research. The costs of publication of this article were defrayed in part by advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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EXPERIMENTAL PROCEDURES

Preparation of the Muscle-PGC-1α/H9251 Construct—The human α-skeletal actin promoter was used to drive skeletal muscle specific expression of a mouse PGC-1α transgene. This promoter is well characterized, and the 2.2-kb fragment used (a kind gift from Drs. E. D. Hardeman and K. Guven at the Children’s Medical Research Institute in Australia) contains all necessary elements for selective expression in the skeletal muscle but not the heart (22). Complete cDNA of mouse PGC-1α was obtained by PCR from first strand cDNA using mouse skeletal muscle total RNA. First strand cDNA was prepared using an Advantage RT-for-PCR kit (Clontech) after DNase I-digestion. For PGC-1α (GenBank accession number AF049330), forward and reverse primer sequences

![Diagram of PGC-1α transgene construct](image)

**Fig. 1.** PGC-1α overexpression decreases GLUT4 expression in skeletal muscles. A, map of the PGC-1α transgene construct used for microinjection of fertilized eggs. B, Northern blot analysis of PGC-1α and GLUT4 mRNAs in several tissues from line B, D, and E transgenic mice (Tg) and their wild-type littermates (WT). Endogenous mouse PGC-1α mRNA (Endo) appears as an upper band (6.5, 5, 3 kb), whereas the transgene of mouse PGC-1α mRNA appears as a lower band (2.8 kb). Arrow indicates the mRNA product from PGC-1α transgene. C, Northern blot analysis of PGC-1α and GLUT4 mRNAs in TA, EDL, and soleus (Sol.) from line B, D, and E transgenic mice and their control wild-type littermates. The -fold change in each mRNA of transgenic mice relative to that of the respective wild-type mice is shown. Ribosomal 18 S RNA on membrane sheet is shown as an RNA loading reference.
were 5'-ATGGCCTGGGAGAAAAAAGATTCAGATT-3'. The PPAR-H11032-accession, L13171): forward, 5'-TATTTAAGAAAAACCTTAAG-3'; reverse, 5'-AACGTCTTCAACCATGACT-3'; medium-chain acyl-CoA dehydrogenase (MCAD) (GenBank accession number M74515): forward, 5'-TCACTTCTTCCACTCATTC-3'; reverse, 5'-TTTAGTGGAACCATTTCTAG-3'.

Preparation of cDNA Probe and Northern Blot—The cDNA fragments for mouse, nuclearly encoded COX subunit IV, medium-chain acyl-CoA dehydrogenase, and NFR-2 (NFR-2-H9251 accession number M37829; forward, 5'-GAGGCTGATGGGCAAGAGGAG-3'; reverse, 5'-TCACTTCTTCCATCTATCTT-3'; medium-chain acyl-CoA dehydrogenase (MCAD) (GenBank accession number U07159; forward, 5'-ATGGCCTACCATTTCCACTAA-3'; reverse, 5'-TTTAGTGGGACACTTCTT-3') with a different copy number were examined; line B (copy number 15), line D (copy number 3), and line E (copy number 1). This construct was expected to direct PGC-1α expression to skeletal muscles. Northern blots probed by 1-H11021 nucleotides of PGC-1α mRNA showed that all these three PGC-1α transgenic mice expressed one transcript (2.8 kb) from transgene PGC-1α mRNA in wild-type mice) of approximately 0.75 milliunits/g of body weight) in fed animals. Blood glucose was measured on samples obtained from the tail tip before and 15, 30, 60, and 120 min after insulin injection. Blood glucose concentrations were measured using TIDEK glucose analyzer (Sankyo, Tokyo, Japan).

Statistical Analysis—The glucose and insulin tolerance curve of each group was compared by repeated measure analysis (Statview 5.0; Abacus Concepts, Inc., Berkeley, CA). When they were significant, each group was compared with the others by Fisher’s protected least-significant-difference test (Statview 5.0; Abacus Concepts). Statistical significance is defined as p < 0.05. Values are mean ± S.E.

RESULTS

Exogenous Mouse PGC-1α mRNA Are Expressed in Skeletal Muscles from Transgenic Mice—Transgenic lines were made with a DNA construct that was composed of 5' flanking skeletal muscles specific regulatory region and promoter of the human α-skeletal actin gene (Fig. 1A). Three lines of transgenic mice with a different copy number were examined; line B (copy number 15), line D (copy number 3), and line E (copy number 1). This construct was expected to direct PGC-1α expression to skeletal muscles. Northern blots probed by 1-H11021 nucleotides of PGC-1α mRNA showed that all these three PGC-1α transgenic mice expressed one transcript (2.8 kb) from transgene PGC-1α mRNA in wild-type mice).

Irrespective copy number, highest expression (13-fold increase compared with 6.5-kb PGC-1α mRNA in wild-type mice) of transgene PGC-1α mRNA in gastrocnemius was observed in line E, second highest expression (10-fold) was in line D, and lowest (1-fold) was line B (Figs. 1B and 4), possibly by a different integration site in mouse genome. These -fold increases are at physiological levels, because exercise training increased all three sized transcripts by 10–13-fold (data not shown).

As described previously, three sizes of endogenous PGC-1α transcripts, 6.5, 5, and 3 kb, possibly caused by utilization of different polyadenylation signals (25, 26), were observed in

overnight at 42 °C with cDNAs, which had been labelled with [32P]dCTP (PerkinElmer Life Sciences) by a random prime labeling kit (Amersham Biosciences). The filters were washed several times with 1× SSC, 0.1% SDS at 42 °C, washed twice at 50 °C, and then exposed to x-ray film at −80 °C. The amounts of each mRNA were quantitated with an image analyzer (BAS 1800; Fuji Film, Tokyo, Japan) and expressed as the intensity of phosphostimulated luminescence.

Oral Glucose and Insulin Tolerance Test—For oral glucose tolerance test, d-glucose (1 mg/g of body weight, 10% (w/v) glucose solution) was administered after overnight fast by stomach tube. Blood samples were obtained by cutting the tail tip before and 30, 60, and 120 min after glucose administration. For insulin tolerance test, human insulin (Humulin R, Eli Lilly Japan K.K., Kobe, Japan) was injected intraperitoneally (0.75 milliunits/g of body weight) in fed animals. Blood glucose was measured on samples obtained from the tail tip before and 15, 30, 60, 90, and 120 min after insulin injection. Blood glucose concentrations were measured using TIDEK glucose analyzer (Sankyo, Tokyo, Japan).

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As described previously, three sizes of endogenous PGC-1α transcripts, 6.5, 5, and 3 kb, possibly caused by utilization of different polyadenylation signals (25, 26), were observed in
skeletal muscles, kidney, heart, brown adipose tissue, and brain. We did not observe the smaller 1.5-kb transcript that was described in the previous study (26). With an increase of exogenous PGC-1α, all three of these endogenous PGC-1α transcripts in quadriceps and gastrocnemius were decreased.

To examine fiber type-specific expression of this construct, expression level of PGC-1α in tibialis anterior (TA), extensor digitorum longus (EDL), and soleus was measured in three lines of PGC-1α transgenic mice (Fig. 1C). Transgene PGC-1α expressed in TA that contains both type I and II muscle, EDL that is type II fiber-rich muscle (white muscle), and soleus that is type I fiber-rich muscle (red muscle). This data indicates that the promoter of the human α-skeletal actin gene drive to both type I and II fibers. As observed in quadriceps and gastrocnemius in Fig. 1B, endogenous PGC-1α mRNA in TA, EDL, and soleus muscles also were decreased.

Gross Changes in PGC-1α Transgenic Mice—The most striking morphological difference was color of glycolytic muscles (Fig. 2). As indicated in the previous study (16), TA, EDL, gastrocnemius, and quadriceps that were rich in type II fibers were paler in appearance in non-transgenic littermates but became dark red in PGC-1α transgenic mice; also, soleus that were originally red and rich in type I fibers became redder in PGC-1α transgenic mice. These color differences in type II fiber-rich muscles were observed in PGC-1α higher expressed, line D and E transgenic mice that express a high amount of PGC-1α but were not observed visually in line B transgenic mice that express a low amount of PGC-1α.

PGC-1α Overexpression Decreased GLUT4 Expression in Skeletal Muscles and Impaired the Insulin-induced Glucose-lowering Effect—Because PGC-1α overexpression increased energy metabolism, it was expected that both lipid and glucose oxidation would be increased. Expression level of GLUT4, a rate-limiting step of glucose oxidation in skeletal muscles, was also expected to increase. Surprisingly, however, overexpression of PGC-1α down-regulated GLUT4 mRNA in gastrocnemius, quadriceps, TA, EDL, and soleus (Fig. 1, B and C). GLUT4 mRNA did not decrease in white adipose tissue, brown adipose tissue, and heart, in which transgene PGC-1α did not express (Fig. 1B).

To examine whether a decrease of GLUT4 mRNA in skeletal muscles affected glucose homeostasis in the whole body, oral glucose tolerance test and insulin tolerance test were made in line D and E mice. In both mice lines, the blood glucose curve after glucose administration did not differ significantly between transgenic and wild-type mice (Fig. 3A). However, the insulin tolerance test clearly demonstrated that the glucose-lowering effects of insulin were lower in PGC-1α transgenic mice compared with their wild-type littermates (Fig. 3B). This unfavorable effect was also observed when the insulin toler-
Fig. 4. PGC-1 overexpression down-regulates MEF2C mRNA. A typical autoradiogram from Northern blot analysis of PGC-1α, GLUT4, and MEF2C in gastrocnemius from wild-type and PGC-1α transgenic mice is shown. Total RNA was isolated, and transferred membrane sheets were probed with 32P-labeled cDNA. The -fold change in each mRNA of transgenic mice relative to that of the respective wild-type mice is shown. Ribosomal 18 S RNA on membrane sheet is shown as an RNA loading reference.

Possible Mechanism(s) for Down-regulation of GLUT4—Transcription factors which regulate GLUT4 in vivo are still unknown, but using muscle cell lines, MFE2C emerged as a possible transcription factor that up-regulates GLUT4 mRNA (27). We examined the possibility that PGC-1 overexpression down-regulates these transcription factors (Fig. 4). In gastrocnemius, with a decrease of GLUT4 mRNA, expression level of MEF2C decreased. Thus, the decrease of MEF2C might contribute to a decrease of GLUT4 expression.

PGC-1α Overexpression in Skeletal Muscles Is Accompanied by Up-regulation of Genes Related to Respiratory Chain Function and Fatty Acid Oxidation—To examine the effect of PGC-1α overexpression on other genes related to energy production, expression levels of genes related to mitochondria, and several target genes of PPARα were measured (Fig. 5). NRF-2, mitochondrially encoded COX subunit II, and nuclearly encoded COX subunit IV increased by 1.1–2.6-fold in three mice lines, parallel with expression levels of PGC-1α. PPARα is a nuclear receptor that regulates the expression of enzymes involved in fatty acid oxidation (28). The mRNAs of PPARα itself and its target gene MCAD (a maker of mitochondrial fatty acid oxidation) increased by 1.6–1.8-fold in mice line D and E that expressed a high amount of PGC-1. However, ACO (a maker of peroxisomal fatty acid oxidation) and LPL, other PPARα target genes, did not increase. ACO and LPL might be regulated by other transcription factors in skeletal muscles. These data suggest that in skeletal muscles from PGC-1α transgenic mice, up-regulation of PGC-1α and its target genes may lead to mitochondrial fatty acid β-oxidation.

DISCUSSION

In contrast to the previous finding in L6 myotubes, in which adenovirus-mediated expression of PGC-1α resulted in a large increase in GLUT4 (18), overexpression of PGC-1α in skeletal muscles did not up-regulate GLUT4; rather, it down-regulated GLUT4 mRNA (Figs. 1 and 4). Because PGC-1α transgenic mice showed red color characteristic of oxidative muscle and up-regulated enzymes related to mitochondrial oxidative phosphorylation and fatty acid oxidation, it was proved that PGC-1α protein derived from the transgene was able to induce mitochondrial biogenesis in skeletal muscles (Figs. 2 and 5). Any discrepancy of PGC-1α effect on GLUT4 expression between these two studies might be related to fundamental differences of GLUT4 expression machinery in vivo and in vitro. Under basal conditions, compared with skeletal muscle tissues, muscle cell lines (L6, C2C12, Sol18) express far less GLUT4 than skeletal muscle tissues, and their insulin responsiveness is minimal (29).

There are several possibilities for the mechanism(s) for down-regulation of GLUT4 mRNA by transgenic PGC-1α. First, endogenous PGC-1α may have at least two forms of PGC-1α protein: a full-length form and a smaller 34-kDa form in skeletal muscles that was identified with the use of a commercially available antibody (20). Although it has not been proven that this small form is derived from PGC-1α mRNA and has some physiological functions, it might up-regulate GLUT4 mRNA. Thus, a decrease in the smaller 34-kDa form might result in a GLUT4 decrease. In this study, we have not measured PGC-1α and GLUT4 proteins in PGC-1α transgenic mice. Because a marked difference of myofibrillar proteins was observed in PGC-1α transgenic mice, it was very difficult to compare the amount of PGC-1α or GLUT4 proteins on a total protein basis between PGC-1 transgenic and their wild-type.
FIG. 6. A proposed model of exercise training induced an increase in mitochondrial biogenesis and GLUT4 in skeletal muscles. Exercise training increases mitochondria and GLUT4 by a different mechanism. Mitochondrial biogenesis and an increase of type I myofibrils are mediated by an increase of PGC-1α, whereas an increase of GLUT4 mRNA is mediated by unknown transcription factors(s). In fasting, increased expression of PGC-1α but not GLUT4 was observed.

littermates. Second, although, it is not known whether MEF2C can up-regulate GLUT4 expression in skeletal muscles as well as in muscle cell lines (27), down-regulation of transcription factors, MEF2C might contribute to a decrease of GLUT4 expression (Fig. 4). Third, a decrease of GLUT4 expression observed in transgenic mice that overexpressed PGC-1α was caused by the secondary effects of a marked rearrangement of myofibrillar proteins (16). Evidence that transgenic mice that overexpressed less PGC-1α (line B) did not up-regulate GLUT4 expression in the absence of a marked phenotypic changes (Figs. 1 and 2) suggests that at least a small PGC-1α overexpression did not up-regulate GLUT4 expression markedly.

Exercise training induced both mitochondrial biogenesis and GLUT4 mRNA in skeletal muscles with an increase of PGC-1α (20, 30). However, our data indicate that PGC-1α overexpression down-regulates GLUT4 mRNA. These findings suggest that exercise training alters other transcription factors that up-regulate GLUT4 mRNA to overcome the PGC-1α effect to down-regulate GLUT4 mRNA (Fig. 6). In liver, PGC-1α plays a key role for gluconeogenesis (31). Because PGC-1α works as an inducer of diabetes in both skeletal muscle and liver, to increase PGC-1α protein or its activity in vivo may not be a good pharmacological intervention for prevention and treatment of diabetes mellitus.

Acknowledgments—We are indebted to Drs. N. Tsuboyama-Kasaoka and T. Nakatani in our laboratory for their helpful discussion.

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J. Biol. Chem. 2003, 278:31385-31390.
doi: 10.1074/jbc.M304312200 originally published online May 30, 2003

Access the most updated version of this article at doi: 10.1074/jbc.M304312200

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