Co-regulation of Tissue-specific Alternative Human Carnitine Palmitoyltransferase Iβ Gene Promoters by Fatty Acid Enzyme Substrate*

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Carnitine palmitoyltransferase I (CPT-I) catalyzes the rate-determining step in mitochondrial fatty acid β-oxidation. CPT-I has two structural genes (α and β) that are differentially expressed among tissues. Our CPT-I β isoform isolates from a human cardiac cDNA library contained two different extreme 5′-sequences derived from short alternative first untranslated exons that utilize a common splice acceptor site in exon 2. Primer extension identified single dominant start sites for each transcript, and ribonuclease protection assays showed the presence of one 5′-exon in liver, muscle, and heart mRNAs, indicating that the cognate promoter U (upstream/ubiquitous) is active in each of these tissues. By contrast, mRNAs containing the alternative 5′-exon were present only in muscle and heart, indicating a muscle-specific promoter M (muscle). CPT-Iβ mRNA levels increased markedly in tissues of fasted rats, when circulating free fatty acid concentrations are elevated. Using CPT-Iβ promoter/reporter transient transfection of murine C2C12 myotubes and HepG2 hepatocytes, fatty acids were found to increase promoter activity in a peroxisome proliferator-activated receptor α (PPARα)-dependent fashion. A promoter fatty acid response element (FARE) was mapped, mutation of which ablated fatty acid-mediated production of both transcripts. PPARα/retnoid X receptor α formed specific complexes with oligonucleotides containing the FARE, and anti-PPARα antibody shifted nuclear protein-DNA complexes, confirming the role of this factor in regulating the expression of this critical metabolic enzyme gene. The constitutive repressor chicken ovalbumin upstream promoter transcription factor competitively binds at the FARE and modulates fatty acid induction of the promoters.

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The carnitine shuttle is utilized in mammalian cells for entry of long-chain fatty acids into the mitochondrial matrix, where they undergo β-oxidation (1, 2). Carnitine palmitoyltransferase I (EC 2.3.1.21; CPT-Iβ) spans the outer mitochondrial membrane and catalyzes the transfer of fatty acyl groups from coenzyme A to carnitine. Acylcarnitines thus formed traverse the inner membrane via a specific translocase, whereupon fatty acyl-CoAs are regenerated by CPT-II within the matrix. This shuttle constitutes the rate-determining process in fatty acid oxidation in all tissues and is highly regulated by virtue of inhibition of CPT-I by malonyl-CoA (1–3). This intermediate is the product of acetyl-CoA carboxylase, the first committed step in fatty acid synthesis, such that reciprocal regulation of synthesis and degradation is effected in liver. Malonyl-CoA is also the major physiological inhibitor of CPT-I in non-hepatic and non-lipogenic tissues, including heart (4–7).

CPT-I has two structural genes (α and β) that are differentially expressed among tissues that utilize fatty acids as fuel. α gene mRNAs are expressed with highest abundance in liver, pancreatic beta cells, and heart, whereas β gene products predominate in skeletal muscle, adipose tissue, heart, and testis (1, 8). The major CPT-I enzymes encoded by these two genes have different kinetic properties, such that the differing relative expression levels among tissues are reflected in different tissue enzyme kinetic properties (1, 2). We have recently described the coexpression of two novel CPT-Iβ mRNA splicing forms in human (8) and rat (9) tissues. These forms constitute only 5–25% of total tissue CPT-I mRNA, but encode enzymes that have altered malonyl-CoA regulatory domains. Thus, changes in fatty acid oxidation rates attributable to CPT-I could result from changes in the following: 1) substrate concentrations, 2) inhibitor (malonyl-CoA) concentration, 3) total α and/or β enzyme mass, 4) relative proportions of α and β enzymes, and 5) relative levels of malonyl-CoA-sensitive and -insensitive enzymes, and therefore through regulation at allosteric, transcriptional, or pre-mRNA splicing levels.

There is a rapid increase in fatty acid oxidation in all tissues in the perinatal period, coincident with initiation of suckling (1, 10, 11). There is also regulation of this pathway in the adult animal, including profound up-regulation during catabolic conditions, when elevated circulating free fatty acid levels result from peripheral lipolysis (1, 2). Regulation at a transcriptional...
level is suggested by parallel increases in fatty acid oxidative enzyme mRNAs in these circumstances (12–14). A direct role for fatty acids in this process is supported by increases in mitochondrial fatty acid β-oxidation enzyme mRNAs in cells cultured in medium supplemented with fatty acids (15–17). Each of these effects has been demonstrated (15) or speculated (16, 17) to be transduced by the peroxisome proliferator-activated receptors (PPARs), nuclear receptor transcription factors that are regulated by fatty acid through derivative metabolites (15, 18–21).

In this study, we evaluated the expression of CPT-Iβ mRNAs in rat tissues in fed and fasted states in order to explore mechanisms of fatty acid oxidation regulation. We show the existence of alternative human CPT-I transcripts that arise from two closely approximated promoters that have tissue-specific or -preferred activities, each of which is alternatively spliced to generate the three previously identified isoforms β1, β2, and β3 (8, 9). A cis-acting element that confers fatty acid regulation of both transcripts is identified that binds and is activated by PPAR/Retinoid X receptor (RXR) heterodimers. Together with our previous findings, these results indicate that there is enzyme substrate-responsive regulated expression of alternative CPT-I mRNA transcripts and alternative pre-mRNA splicing variants in tissues.

**EXPERIMENTAL PROCEDURES**

**Genomic Cloning—** A P1 clone was obtained (Genome Systems, St. Louis, MO) by hybridization screening with previously isolated human CPT-Iβ1 cDNA (8). A MluI-AvrII fragment corresponding to 5′–5–kilobase upstream of the exon 2 splice acceptor was cloned into pBS cloning a 5′-untranslated region sequences (Fig. 1) and is the same length as UcDNA, indicated that the major start codon adenine. Similarly, assays using UcDNA, which was isolated and cloned into pBS for use in generating hM2 and hU2 mRNA probes. Templates for hM2 and hU2 cRNA probes may be produced by using a synthetic idealized late promoter (25). Mobility shift assays were performed (15, 25, 26) using a 32P-end-labeled oligonucleotide S1 (f = 5′-gatcc.gacgTGACCTTCTTCCCAatctggtagctttctcatacttc.a-3′; r = 5′-gatcc.tagatgtaaaatagccacatagAGGGAAAgGTTGCAccgt-3′) and competition with S1, S2 (r = 5′-gatcc.tttgatgttagctttctcatacttc.a-3′) and r = 5′-gatcc.tagatgtaaaatagccacagc.g-3′) or a non-specific probe competition.

**RESULTS**

**Alternate Human CPT-Iβ Transcripts Exist—** The presence of two divergent sequences at the 5′-end of our CPT-Iβ isoforms from a human cardiac cDNA library (Fig. 1a) suggested the possibility of alternative gene promoters. CPT-Iβ structural gene sequence (27) indicated that our cDNAs correspond to alternative 5′-exons (Fig. 1c). Using human heart and skeletal muscle total RNAs, we performed primer extension assays to determine transcription start sites (TSSs). Reactions with an antisense primer corresponding to sequence within exon M (M(1 DNA)) (Fig. 1b, right panel) gave one strong product, indicating a single start site for this transcript at +523 relative to the initiation codon adenine. Similarly, assays using U(1 DNA) (Fig. 1b, left panel) gave several minor upstream U TSSs between +710 and +745. Both 5′-exon splice donor signals and the exon 2 acceptor sequence corresponding to the consensus sequence (28) (Fig. 1d). RPs and polymerase chain reaction-based analyses failed to detect the existence of mRNAs corresponding to previously reported CPT-Iβ transcripts that extend immediately 5′ of exon 2 (29) and excluded use of the 5′-untranslated exons in combination. Neither full-length mRNA contains an AUG codon upstream of that found in exon 2. Thus, the human CPT-Iβ gene has two closely ap-

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proximated promoters that give rise to mRNAs with an identical initiation codon.

Alternative CPT-Iβ Promoters Are Differentially Utilized among Tissues—Variable intensity of primer extension products in reactions using various tissue RNAs suggested differing relative abundance of the two CPT-Iβ mRNA transcripts among tissues. To further evaluate this and as a first step in analyses of regulation of the promoters, we performed RPAs with human tissue RNA using cRNA probes that spanned the transcript-specific splice junctions. Thus, the Mβ probe was derived from a cDNA containing exon M, whereas the Uβ probe contained the exon 5′-9 sequence (Fig. 2a). In assays with human heart RNA, two protected probe fragments were obtained when using each probe (Fig. 2b, H lanes). Protected fragments of the Mβ probe corresponded to mRNA derived from the M transcript (Mβ) and from one or more different transcripts with alternative 5′ exons spliced to exon 2 (β). Similarly, the pattern of Uβ probe protection was consistent with the presence of the U transcript mRNA (Uβ) as well as alternative(s) (β). A similar pattern was seen in RPAs using skeletal muscle RNA (Fig. 2b, S lanes), although the ratio M:U was 2:1, unlike the 4:1 ratio in heart. In contrast, a >20:1 preference of U transcript-derived mRNA was present in liver (Fig. 2b, L lanes) as well as in pancreas (data not shown). The relative intensities of the two Mβ probe bands were reciprocal to those of Uβ (i.e., [Mβ/Uβ]Mβ = [β/β]Uβ, indicating that any possible additional transcripts in which other upstream exons splice into the exon 2 acceptor could contribute only a very minor fraction to the total CPT-Iβ mRNA in the tissue samples. Thus, the two alternative CPT-Iβ promoters, M (muscle) and U (upstream, ubiquitous), show tissue-specific or -preferred utilization, and these are the major promoters active in the tissues examined.

Both CPT-Iβ Transcripts Are Alternatively Spliced—We have previously described alternative splicing of human (8) and rat (9) CPT-Iβ pre-mRNAs that gives rise to β1, β2, and β3 isoforms. β3 mRNA results from exon 5 skipping and represents a minor component of human and particularly rat total
CPT-Iβ mRNAs in tissues. β2 message is derived from use of a cryptic exon 3 splice donor in combination with exon 4 skipping and contributes 5–25% of total tissue CPT-Iβ. Expression of these mRNAs also shows tissue preference (8), and all independent human β3 cDNA isolates contained exon M sequence. To explore whether these findings reflected differential splicing pattern preference of the alternative transcripts, we performed RPAs using cRNA probes that spanned both the M or U transcript-specific splice junction and the β2 isoform-specific seam (Fig. 3a). These assays indicated that both the M and U transcripts are alternatively spliced to generate β1 and β2 mRNAs (Fig. 3b). The splicing patterns that give rise to the six CPT-Iβ mRNAs are depicted in Fig. 3c.

**Tissue CPT-Iβ Gene Expression Is Up-regulated with Fasting**—We examined the influence of fasting on steady-state CPT-Iβ mRNA levels in rat myocardium, skeletal muscle, and liver. Under these catabolic conditions, circulating free fatty acid concentrations are elevated due to peripheral lipolysis, and fatty acid oxidative activity is brisk in these tissues (2, 30, 31). As shown in Fig. 4, in 2- and 5-day fasted rats, there was a marked increase in steady-state CPT-Iβ mRNA levels in each tissue compared with those in rats fed ad libitum as determined by RPA. Increases in each CPT-Iβ isoform mRNA occurred with the fast, although the relative proportions of these messages appeared to change, particularly in liver (data not shown). Thus, there is a coordinate increase in both malonyl-CoA-sensitive (β1) and -insensitive (β2) CPT-I expression under catabolic conditions, and this is likely to contribute to the observed accelerated fatty acid β-oxidation rates.

**Fatty Acids Regulate CPT-Iβ Gene Expression through PPARα Activation**—To begin to evaluate the mechanism of the observed effect on CPT-Iβ mRNA in vivo, we performed transient transfection experiments with C2C12 myotubes, HepG2 hepatocytes, and other cell lines. For initial studies, a fragment of the human CPT-Iβ gene extending from −1 to −1062 relative to the initiation codon adenine was fused to a luciferase reporter gene to generate U/M/Int1-LUC (Fig. 5a). This reporter includes both the M and U TSSs and retains the first intron (Int1) and the exon 2 splice acceptor. Because circulating counter-regulatory hormone and free fatty acid concentrations are elevated with fasting compared with the fed state, we first evaluated the influence of these factors. Glucagon, adrenergic agonists, and adenylate cyclase activators did not affect U/M/Int1-LUC activity. However, small but reproducible effects were seen when transfected cell culture medium was supplemented with fatty acids such as oleate. Fatty acids can regulate transcription through the PPAR nuclear receptor transcription factors. Since the PPARα isoform is the dominant isoform in these tissues (15, 21), we evaluated the role of PPARα in mediating fatty acid-induced CPT-Iβ promoter activity using cotransfection of C12,C12 myotubes. As shown in Fig. 5b, cotransfection of PPARα produced a 17-fold activation of the promoter when incubated in medium stripped of low molecular weight hydrophobic moieties, including fatty acid acids and retinoids (15, 26). This apparent constitutive PPAR activity is attributable to activation of this transcription factor by endogenous fatty acids, as is typically seen (15, 19, 26). Fatty acid-mediated CPT-Iβ promoter activation up to 50-fold above basal activity was seen in PPARα-cotransfected cells incubated in medium supplemented with long-chain (oleate, C18:1) and medium-chain (decanoate, C10:0) fatty acids as well as gemfibrozil, POGA (a CPT-I inhibitor) (1, 15), and the PPARα-specific agonist (8S)-hydroxycocetosteroenic acid (19).

**Fatty Acids Co-regulate the U and M Transcripts**—To evaluate differential or co-regulation of the U and M transcripts by fatty acids as well as other factors, we constructed additional reporters (Fig. 5a). In U-LUC, the U promoter is fused to the correctly spliced untranslated portions of exons U and 2 and to a luciferase reporter gene. M-LUC contains the structural gene sequence 5’ of the M TSS fused to the untranslated portions of exons M and 2 and the luciferase gene. PPARα activated both U-LUC (12.4-fold) and M-LUC (9.6-fold) in transfected C12 cells (Fig. 5c), and these activations were not significantly different from that seen with U/M/Int1-LUC. Independent confirmation of co-regulation of the promoters was provided using assays of RNA obtained from cells transfected with U/M/Int1-LUC with or without PPARα cotransfection. Here, coordinate increases in the intensity of protected probe bands corresponding to exons M and U were visualized (data not shown). These studies also confirmed correct exon U/2 and M/2 splicing of the plasmid reporter-derived mRNA. Our results indicate that the
two promoters are co-regulated by fatty acids through PPARα activation, consistent with the observed elevations in CPT-1β mRNA levels in heart, skeletal muscle, and liver. Furthermore, the cis-acting FARE responsible for this activity is necessarily located 5′ of the U TSS. The CPT-1β FARE is a Prototypical DR1 Nuclear Receptor Response Element—The CPT-1β gene FARE was mapped using a U-LUC 5′-deletion series. PPARα activation was maintained in constructs deleted for promoter sequences to −787 or a mere 85 base pairs from the U TSS (Fig. 6a). Inspection of gene sequence in this region revealed the existence of an antisense consensus nonsteroid-type nuclear receptor binding site, AGGTCA (32). Flanking sequence was compatible with an imperfect direct hexamer repeat with single base pair separation (DR1; AGGGAAcAGGTCA) that might be permissive for receptor binding and activity (Fig. 6b). An analogous reporter (ULUC) containing dinucleotide substitution within the consensus hexamer (AGGGAAcAGGTCA) had unchanged basal reporter activity, but failed to respond to PPARα or fatty acids (Fig. 6c). Identical FARE substitution mutations in the other reporters (U/M/Int1-LUC and M-LUC) also abrogated PPARα responsiveness. Thus, the CPT-1β M and U transcripts are co-regulated from a single necessary and sufficient element centered at −789 relative to the AUG initiation codon, 67 base pairs upstream of the major U TSS and 246 base pairs upstream of the M TSS. In muscle cells, the basal activity of M-LUC was virtually identical to that of U/M/Int1-LUC, whereas that of U-LUC was substantially lower. Full maintenance of activity in M-LUC as compared with U/M/Int1-LUC indicates that there is no influence of intron 1 sequences on promoter activity in myocytes.
DR1 PPAR response element of the ACO gene promoter (35) in HepG2 cell cotransfections. CPT-I β-U-LUC failed to respond to the RXR-specific retinoid ligand LG69, even with RXRα cotransfection (Fig. 9a), whereas this ligand stimulated the MCAD (Fig. 9b) and ACO (data not shown) elements in an RXR-dependent manner. There was some constitutive PPARα activity on all elements, but this was most robust for the CPT-I β FARE. Each element showed additive activities of PPAR- and RXR-specific activators/ligands in PPAR-cotransfected cells. However, overexpression of RXR unexpectedly severely blunted CPT-I β promoter activity while potentiating PPAR stimulation of the ACO and MCAD elements, indicating that CPT-I β FARE element structure dictates novel regulatory properties.

**DISCUSSION**

We have demonstrated that the human CPT-I β gene has two transcripts that generate mRNAs with differing 5′-untranslated regions. These transcripts show tissue-enriched or -specific expression, and each is alternatively spliced within the coding region. One transcript is present in heart and muscle (M), whereas the other is ubiquitously (U) expressed in tissues with high fatty acid oxidation rates. Fatty acids regulate production of both transcripts through activation of PPARα, which binds as a heterodimer with RXR on a FARE located in the proximal U promoter region. The physiological significance of this regulation is reflected in a robust increase in CPT-I β mRNA levels in rat tissues under catabolic conditions, when elevated circulating free fatty acids are presented as fuel and are available to activate gene expression.

Both the CPT-I β U and M promoters are TATA-less. This is somewhat surprising, as this feature is more typical of “housekeeping” genes and those whose products are required early in development (37). The M promoter does have two proximal GC boxes that may facilitate transcription factor IID binding and RNA polymerase II activity (37, 38). The location of the major U transcript TSS at −702 differs from that previously reported by Yamazaki et al. (39), who suggested that it was located at −745 based on 5′-rapid amplification of cDNA ends. Although we saw no band consistent with this start site using primer extension, RPA did confirm this and other secondary start sites between −702 and −745. Alternative U transcript start sites are of interest because additional functional regulatory elements overlap or are contained within the −702 to −745 region. Furthermore, the FARE is located a mere 18–30 bases upstream of the −745 TSS, where it would be expected to interfere with the binding of polymerase II components. The existence of numerous proximal U promoter regulatory elements in the absence of a TATA box suggests that regulated activities of cognate factors may influence the precise locus of polymerase II binding as well as its activity.

Although the U and M TSSs are closely approximated, the existence of mutually exclusive first exons, as well as preferential utilization among tissues, indicates that these are bona fide alternative promoters. Vigorous M promoter activity in muscle and heart, but not in liver and nonmuscle tissues, has two mechanistic explanations. First, muscle-specific factors may transactivate cis-acting elements that selectively control the M promoter. Alternatively, factors in nonmuscle cells may transrepress to eliminate M promoter activity. Candidate elements include GC boxes in the proximal M promoter, which may regulate gene expression through Sp1/Sp3 competition, for example (37, 40, 41). However, regardless of mechanism, the distinction of M and U promoters does not dictate that element(s) that specifically regulate M expression are necessarily located only in the region between the two TSSs. Pertinent to
this is the existence of a conserved E box and a consensus myocyte enhancer factor-2 site in the proximal U promoter region of human and rat genes. The activity of the FARE indicates that that the converse also applies: a cis-acting element within the U promoter is capable of controlling both promoters. Differential regulation of CPT-Iβ M and U promoters by various transcription factors, functioning alone or through cooperative interactions, may ramify in altered CPT-I enzyme kinetics through preferential transcript splicing patterns (see below).

We have recently described alternative mRNA splicing within the coding region of CPT-Iβ (8, 9). β2 and β3 mRNAs are produced by cryptic splice donor utilization and/or exon skipping and encode enzymes that are deleted for a transmembrane domain or an adjacent region that is necessary for physiological allosteric regulation of CPT-I by malonyl-CoA (1, 42). Because of precedent for differential splicing patterns of alternative transcripts (28), we investigated this possibility for this gene. Although we demonstrate that both the M and U transcripts are alternatively spliced, we cannot exclude the possibility that coding region alternative splicing is co-regulated with alternative promoter utilization or activity. However, even if this is true, the relative abundance of mRNAs containing M versus U exons and of β1 versus β2 versus β3 mRNAs in heart, muscle, and liver (8) indicates that alternative splicing is also independently regulated.

During the preparation of this manuscript, Mascaro et al. (43) reported regulation of the CPT-Iβ promoter by PPARα and PPARγ isoforms and cognate activators in cotransfected CV1 cells. These investigators mapped the identical FARE, but found less vigorous PPAR effects (3–4-fold) than we report here, possibly due to the different transfected cell type. Regulation of the alternative promoters was not addressed, and PPAR isoform-specific activators were evaluated rather than PPAR isoform-specific activators were evaluated rather than the ordinary dietary and endogenous fatty acids of our study. Although much recent attention has focused on high affinity isoform-specific PPAR ligands (19, 20, 44), activities of oleate and palmitate at concentrations that are routinely achieved in the circulation suggest that the physiologically relevant activators of PPARα are these common fatty acids, regardless of the higher affinity of rare metabolites, as we have previously suggested (15). This point is underscored by the demonstrated efficacy of decanoic acid in activating PPARα on this FARE. Since medium-chain fatty acids make up a major component of milk, this implies a role for this factor in the observed up-regulation of CPT-I and other genes encoding fatty acid oxida-
tive enzymes during suckling (12–14).

The CPT-Iβ FARE sequence conforms to the conventional PPAR/RXR DR1-type element (26, 32), and although the 5′-half-site (antisense AGGGAA) deviates from the consensus sequence, its flanking region is A/T-rich, consistent with the structure of other PPAR response elements (45). There are unique features of this element with respect to RXR and retinoid activities compared with other DR1 and complex elements, as exemplified by those of the ACO (35) and MCAD (15) genes, respectively. For these and other previously described elements (26, 35), both PPAR and RXR are cognate ligand-responsive, and the receptors function cooperatively. In the case of the CPT-Iβ FARE, despite cooperative binding of the receptors, overexpression of RXR attenuates PPAR and fatty acid responsiveness. Furthermore, the FARE is not activated by the RXR-specific ligand LG69 (36) in the absence of PPAR

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Note Added in Proof—Brandt et al. (52) recently reported similar findings.

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