Human Acetyl-CoA Carboxylase 2

MOLECULAR CLONING, CHARACTERIZATION, CHROMOSOMAL MAPPING, AND EVIDENCE FOR TWO ISOFORMS

(Received for publication, December 3, 1996, and in revised form, February 4, 1997)

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Acetyl-CoA carboxylase (ACC), a biotin-containing enzyme, catalyzes the carboxylation of acetyl-CoA to malonyl-CoA, the rate-limiting step in fatty acid synthesis. Malonyl-CoA is the C₂ donor in the de novo synthesis of long chain fatty acids and in their elongation into very long chain fatty acids (1, 2). Malonyl-CoA is also involved in the synthesis of polyketides (3), and there are indications that it may be involved in the synthesis of an as yet unknown compound or pathway (4, 5). Moreover, Malonyl-CoA is a regulator of the palmitoyl-CoA-carnitine shuttle system that is involved in the mitochondrial oxidation of long chain fatty acids (6).

ACC is a complex multifunctional enzyme system. In prokaryotes, it is composed of three distinct and separable proteins: the biotin carboxyl carrier protein, the biotin carboxylase, and the transcarboxylase. In eukaryotes, however, the individual proteins of ACC are associated with a single multifunctional polypeptide (Mₓ, 265,000) that is encoded by a single gene. We prefer to refer to this form of ACC as ACC1. The cDNAs coding for the yeast (7), rat (8), chicken (9), and human (10) ACC1 carboxylases have been cloned and sequenced. The predicted amino acid sequences of the ACC1 carboxylases are very similar, there being a greater than 90% identity among the animal ACC1 carboxylases and about 35% similarity between the animal and yeast ACC1 carboxylases. They immunologically cross-react with each other. The ACC1 carboxylases are highly enriched in lipogenic tissues and are under long term control at the transcriptional and translational levels and under short term regulation by the phosphorylation/dephosphorylation of targeted serine residues and by allosteric transformation by citrate or palmitoyl-CoA (11–17). The levels and activities of the ACC1 carboxylase in lipogenic tissues fluctuate in response to both the dietary and hormonal states of the animal. Starvation or diabetes reduces the activity of ACC1 by repressing the transcription of the gene ACC1 or by increasing the phosphorylation levels of the protein ACC1 (or both). On the other hand, refeeding animals, especially a carbohydrate-rich, fat-free diet, or treating diabetic animals with insulin induces the synthesis of the ACC1 carboxylase and increases its activity either by dephosphorylation of the protein or by activation with citrate.

Another carboxylase (ACC2) from rat heart, a tissue in which little or no fatty acid synthesis takes place (18, 19), was discovered in our laboratory by Thampy (20) and purified to a homogeneous state. The ACC2 carboxylase has a molecular weight of 280,000, has biotin as a prosthetic group, and responds to phosphorylation/dephosphorylation and citrate activation in a manner similar to ACC1 (20). Anti-ACC1 antibodies do not significantly inhibit the activity of ACC2, nor do they
bind to the protein in a Western blot test (20), suggesting that the two enzymes are different although they catalyze the same reaction and have very similar sequences (see below). These differences were reinforced by the fact that ACC2 is also present at relatively high levels in skeletal muscle (21, 22). Moreover, ACC2 is also found in rat liver (23) and in human liver (this study). Studies with rat liver ACC1 and ACC2 showed that the two isoforms do not cross-react immunologically although the amino acid sequences of 12 randomly isolated peptides from each carboxylase show a high degree of similarity (~70%) (23).

The physiological role of ACC2 is not clear at this time. Nevertheless, the presence of ACC2 in heart and muscle as the predominant form of carboxylase has led many investigators to propose that ACC2 and its product malonyl-CoA are involved in the regulation of fatty acid oxidation by these tissues (20, 21, 24).

Attempts to identify the rate of fatty acid oxidation in newborn and ischemic hearts with carboxylase activities and malonyl-CoA levels led to the conclusion that fatty acid oxidation in the heart is inversely related to carboxylase activities, a correlation that is compatible with the notion that ACC2 is present in heart and muscle tissues for the purpose of regulating fatty acid oxidation (25, 26). To understand the structure-function of ACC2 and its relationship to ACC1, we isolated ACC2 cDNA from human liver and sequenced it. Herein, we report the complete sequence of the cDNA encoding the human ACC2 carboxylase and the chromosomal localization of its gene. We also show the distribution of ACC2 in various human and mouse tissues and provide evidence for the presence of an isoform of ACC2 in human liver.

EXPERIMENTAL PROCEDURES

**Materials**—Klenow DNA polymerase, T4 polynucleotide kinase, T4 DNA ligase, and all restriction enzymes were purchased from New England Biolabs (Beverly, MA). Taq DNA polymerase was purchased from Perkin-Elmer. The sequencing kits for the dyeoxy chain termination method were purchased from U.S. Biochemical Corp. 32P- or 35S-labeled nucleotides were purchased from Amersham Corp. Human liver 5’-RACE-ready cDNA, human liver poly(A)+ mRNA, human and mouse multiple-tissue Northern blots, and the TALON purification system were obtained from Clontech Laboratories, Inc. Alkaline phosphatase-conjugated secondary antibodies, nitro blue tetrazolium, and 5-bromo-4-chloro-3-indolyl phosphate were purchased from Promega, Inc. Reagents, antibodies, nitro blue tetrazolium, and 5-bromo-4-chloro-3-indolyl phosphate were obtained from Clontech Laboratories, Inc. Alkaline phosphatase-conjugated secondary antibodies, nitro blue tetrazolium, and 5-bromo-4-chloro-3-indolyl phosphate were purchased from Promega, Inc. Reverse transcriptase and the random primer labeling kit were purchased from Stratagene. The Western blot kit was from Novagen. All oligonucleotides were synthesized using a Beckman Oligo 1000 DNA synthesizer. All other chemicals used were of the highest quality commercially available.

**General Molecular Biological Methods**—Standard molecular biological techniques were employed (27). cDNA clones were sequenced by using the dyeoxy chain termination method (28) and a Sequenase T7 DNA polymerase kit. First-strand cDNA was synthesized from poly(A)+ mRNA by reverse transcription with oligo(dT) primers as described (27). Northern analysis was carried out on the human and mouse multiple-tissue blot according to the manufacturer’s recommendations.

**PCR Quantitation of ACC2 Isoforms in Human Liver**—Given the difficulty in distinguishing, in a Northern blot, between 10-kb mRNA and 5.5-kb mRNA, we used reverse transcriptase-PCR methods to amplify the ACC2 cDNA fragments. We used first-strand cDNA and 5’-RACE-ready PCR cDNA from human liver as templates. To isolate the 2.4-kilobase pair 3’-end cDNA (clone g; Fig. 1), we used a forward primer (5’-AATGAGTTGCGGTAGTGGGCC-3’ (nucleotides 5371–5391)) based on the published sequence of Ha et al. (31) and a reverse primer (5’-GACGCCGCGCCCTCACCTGA-3’ (nucleotides 7432–7452)). Amplification reactions were carried out on a PTC-100 programmable thermal controller (MJ Research, Inc.) by varying the time and temperature as follows: 94 °C for 1 min, 55 °C for 1 min, and 72 °C for 2 min, followed by a 10-min elongation step at 72 °C. The amplified PCR products were then separated by agarose gel electrophoresis. The bands with the expected size were extracted, treated with T4 polynucleotide kinase, and subcloned into the Smal or EcoR restriction site of pBluescript II KS+ vector (Stratagene). The subcloned cDNA fragments were sequenced from both ends by using T7 DNA polymerase kits. Although the sequence of clone g was identical to that of the abdominal fat ACC cDNA, it had less than 60% identity at the nucleotide level with its counterpart of the human ACC1 cDNA (10).

To extend the 5’-end of clone g (Fig. 1), we used first-strand cDNA and 5’-RACE-ready PCR cDNA synthesized from commercially available human liver poly(A)+ mRNA (Clontech) as a template. Briefly, a single-stranded anchor oligonucleotide (5’-CACCCTTGCGATGGAGTTGGTTGCC-3’ (nucleotides 5460–5486)) that was ligated to the 5’-end of human liver cDNA was used as the forward primer, and a second oligonucleotide (5’-GGCCCAAGTTCAATGGGAAAGGTG-3’), corresponding to the 5’-end of clone g (Fig. 1), was used as the reverse primer. Several overlapping clones, each ranging from 500 to 1,000 bp in size, were isolated, subcloned, and sequenced. Clone f contained the longest cDNA fragment (Fig. 1).
Clones d and e (Fig. 1), each of which contained the highly conserved biotin-binding site, were isolated with a degenerate forward primer (5′-ATNGANGTNATGAAA/GATG-3′) that was based on the sequence of human ACC1 (10), which includes the Met-Lys-Met codons at the 3′-end, and a reverse primer (5′-CCGACGAACTTCCATTGTG-3′ (nucleotides 4449–4467)) from clone f (Fig. 1). Using these two primers and first-strand cDNA as a template, we amplified two cDNA fragments, one 1.6 kb in length (clone d) and the other 1.3 kb in length (clone e) (Fig. 1). Subcloning and sequencing these two fragments revealed that their sequences are identical. However, 303 nucleotides that encode 101 amino acids are present in the 1.6-kb fragment but absent from the 1.3-kb fragment.

To extend our cloning upstream of clones d and e, we used the same cloning strategy employed above. In this case, however, we prepared a degenerate forward primer (5′-TCNC/AYC/GGNGA/A/G/TG/TGT/CGTNAC-3′) that was based on the amino acid sequence of peptide 17, which was reported by Winz et al. (23) and was present in both the rat ACC1 and ACC2 isoforms. Using this primer together with a reverse primer (5′-CCCTTCTAAGTGCCACCCGGCTGAA-3′ (nucleotides 2890–2913)) derived from clone d, we amplified a 2.1-kilobase pair cDNA fragment (clone c; Fig. 1). Nucleotide sequencing of this clone revealed a high degree of similarity with the corresponding region of the human ACC1 cDNA. Finally, two overlapping cDNA clones, a (900 bp) and b (950 bp), which extended up to the first Met codon, were obtained by using the 5′-RACE-ready PCR cDNA technique used above with a reverse primer (5′-GGTTTGTTCGCATGGTGACCCCC-3′) that was based on the sequence of human ACC1 (10), which includes the Met-Lys-Met codons at the 3′-end, and a reverse primer (5′-CCTTCTAAGTGCCACCCGGCTGAA-3′ (nucleotides 878–900)) derived from clone c. Both clones contained sequences from the 5′-untranslated region and the first ATG, which was preceded by two TGA stop codons, suggesting that this ATG is the first translation codon.

**Analysis of the Deduced Amino Acid Sequences of Human ACC2**—The nucleotide sequence of the cDNA of the human liver ACC2 carboxylase has an open reading frame of 7,449 nucleotides (Fig. 2) that encode 2,483 amino acids with a calculated molecular weight of 279,330, which is close to the 280-kDa mass estimated for the carboxylase isoform isolated from rat heart, skeletal muscle, and liver (20, 21) and from human liver. We readily identified the highly conserved biotin-binding site (Met-Lys-Met), the putative ATP-binding site of the biotin-carboxylase partial activity, and the CoA-binding site (Met-Lys-Met), the putative ATP-binding site of the biotin-carboxylase partial activity, and the CoA-binding site (Met-Lys-Met). Using the 400-bp PCR clone that encodes the N-terminal region of ACC2 cDNA, we isolated two cDNA clones, d (1.6 kb) and e (1.3 kb) (Fig. 1), that had identical sequences, except for a segment of a polypeptide of 30 amino acids that are present in clone d and absent in clone e.

**Expression of ACC2 in Various Human and Mouse Tissues**—Using the 400-bp PCR clone that encodes the N-terminal region of ACC2 as a specific probe for ACC2, we performed Northern blot analyses of mRNAs from various human and mouse tissues. Our results showed that the probes hybridized to a major (~10-kb) mRNA band and to a smaller (9-kb) band (Fig. 5). We believe that the shorter band does not represent the 270-kDa ACC isoform, because both bands hybridized with the 300-bp ACC2 as Ser219 and Ser221, as evidenced by the high degree of similarity in the amino acid sequences between ACC1 and ACC2 at and immediately downstream from these serines (Fig. 3). However, Ser1200 of rat ACC1 (Ser1201 of human ACC1 (10)), which has been implicated in the phosphorylation and regulation of ACC1 (12), apparently is not conserved in human ACC2 (Fig. 3). In fact, the amino acid sequences in this region show that there is little similarity between the two ACC isoforms and that some amino acids in the ACC1 polypeptide are deleted from ACC2 (Fig. 3). As discussed above, during the cloning of the full-length human liver ACC2 cDNA, we isolated two cDNA clones, d (1.6 kb) and e (1.3 kb) (Fig. 1), that had identical sequences, except that the shorter clone lacked the 303 nucleotides that encode 101 amino acids between Arg1114 and Asp1215 (Fig. 2). The complete identity between the nucleotide sequences of the two clones in the overlapping regions suggests that these clones are the product of an alternate splicing mechanism and may represent two ACC2 isoforms, one 280 kDa and another 270 kDa. To rule out a cloning artifact and to estimate the abundance of both ACC2 mRNA isoforms, we used reverse transcriptase-PCR methods (32) and Southern blot analysis as stated under “Experimental Procedures.” As expected, we amplified two cDNA fragments, 1.1 and 0.8 kb (Fig. 4, lane 2). Using the 400-bp cDNA fragment located downstream of Asp1215 as a probe in Southern blot analysis and scanning the intensities of the blots showed that the 280-kDa ACC2 isoform is three times more abundant than the 270-kDa isoform (Fig. 4, lane 3). At this stage, we cannot rule out other differences between the sequences of the 280- and 270-kDa isoforms. We were unable, however, to isolate other cDNA clones that had such differences in their sequences. Comparing the peptide of the 101 amino acids that are missing from the 270-kDa ACC2 isoform with its counterpart in ACC1 showed a high degree of sequence identity except for a segment of a polypeptide of 30 amino acids that are absent in ACC1 (Fig. 3).
Fig. 2. Nucleotide sequence of the human liver ACC2 cDNA and the predicted amino acid sequence of the protein. The numbering shown is for the nucleotide and amino acid sequences. The conserved Ser219 and Ser221, which are equivalent to the Ser77 and Ser79 of rat ACC1 and are implicated in activity modulation of ACC1 by phosphorylation/dephosphorylation, are indicated in boldface type. The putative nucleotide binding motif, the biotin-binding site, and the putative CoA-binding site are also indicated in boldface type. The nucleotide sequences of the 303 bp that are absent from the 270-kDa human liver ACC2 isoform are underlined.
PCR fragment that is present in clone d but not in clone e (data not shown). The two bands, therefore, may represent transcripts that differ in the noncoding region. The 400-bp cDNA probe hybridized to the mRNAs of ACCs from human and mouse hearts, livers, and skeletal muscles and was expressed in a similar pattern (Fig. 5), suggesting that ACC2 is conserved in human and mouse tissues. In comparing the muscle tissues of human organs, the heart and skeletal muscle have higher levels of ACC2 mRNA (Fig. 5B). The high levels of ACC2 mRNA in heart and muscle tissues are consistent with the earlier findings of high levels of ACC2 in rat heart and muscle (20, 33).

Chromosomal Localization of the ACC2 Gene—Previously, we mapped the gene that encodes human ACC1 to chromosome 17q21 (10). When we compared the cDNA sequences of the 265- and 280-kDa ACC isoforms, it became apparent that they most probably are not products of the differential splicing of a single gene. To localize the gene that encodes the 280-kDa human

Fig. 2—continued
ACC, we performed fluorescence in situ hybridization of a biotin-labeled cDNA probe (5 kb) to normal human metaphase chromosomes. Hybridization of this probe resulted in specific labeling of only chromosome 12q23.1 (Fig. 6). These results are the first direct evidence that the 265- and 280-kDa human ACC isoforms are the products of two separate genes, ACC1 and ACC2.

Fig. 3. Comparison of the deduced amino acid sequences of human ACC1 (10) and human ACC2. The sequences were aligned by using the Bestfit program of the GCG software package. The amino acids are identified in single-letter code, and the gaps ( . . . ) are introduced to optimize the alignment. Those amino acid residues that match exactly are identified by vertical lines. Residues that are less similar are identified by a dot, and those that are more similar are identified by a colon. The serines that apparently are linked to the activity modulation of ACC in rat liver, the putative nucleotide-binding site, the biotin-binding site, and the putative CoA-binding site are indicated in boldface type. The arrow between Arg1114 and Asp1215 in the ACC2 sequence indicates the missing 101 amino acids in the 270-kDa ACC2 isoform.
Expression of the N-terminal cDNA in Escherichia coli and Preparation of Specific Polyclonal Antibodies—To produce polyclonal antibodies that would recognize only the ACC2 protein, we cloned a cDNA fragment (nucleotides 1–666) that encodes the N-terminal variant region of ACC2 into the PET plasmid and expressed it in BL21 E. coli as a thioredoxin fusion protein (Fig. 7). The soluble fusion protein was purified using a TALON affinity column and eluted with 100 mM imidazole. The highly purified fusion protein (Fig. 7C) was used to raise antibodies in rabbits. These polyclonal antibodies recognized human ACC2 but not human ACC1 (data not shown). They also cross-reacted with rat liver ACC2 but not with the more abundant rat liver ACC1 as shown in a Western blot (Fig. 8, lane 3). These results, together with the Northern blot analyses of mRNAs of human and mouse tissues displayed in Fig. 5, clearly show that this ACC isoform is highly conserved at both the nucleotide and the amino acid levels and is expressed in a tissue-specific manner. Interestingly, antibodies raised against human ACC1 purified from HeLa cells recognized rat liver ACC1 but not rat liver ACC2, despite the high degree of homology between the two proteins (Fig. 8). Similar observations were made by Thampy (20) and by Witters et al. (33), who reported that antibodies raised against the 265-kDa rat liver ACC did not recognize the 280-kDa rat ACC isoform. As expected, both ACC1 and ACC2 reacted strongly with avidin peroxidase, indicating that they are indeed biotin-containing enzymes (Fig. 8, lane 4).

DISCUSSION

It has long been suggested that the multiple forms of ACC detected by SDS-PAGE are the products of limited proteolysis or occur as the result of differential splicing mechanisms. Although it is nearly impossible to isolate only one form of ACC from animal tissues, several lines of evidence indicated the existence of at least two ACC isoforms, the 265-kDa (ACC1) and the 280-kDa (ACC2). Although both ACC1 and ACC2 contain covalently bound biotin as the prosthetic group, ACC1 is immunologically distinct from ACC2 (20, 21, 33). The two isoforms also exhibit different kinetics toward the substrate acetyl-CoA (33). The data reported herein, including the chromosomal localization, provide the first direct evidence that ACC1 and ACC2 are the products of two separate genes.

Comparing the predicted amino acid sequences of ACC1 and ACC2 showed the presence of an additional 142 amino acids at the NH2 terminus of ACC2 that may account for the difference in molecular weight and may be involved in targeting the ACC2 protein toward a specified cellular membrane or membranes. Examination of the hydrophatic profile of the predicted amino acid sequence of the NH2-terminal region of ACC2 (residues 1–140) by using the Kyte-Doolittle algorithm (34) and of the secondary structure predicted according to the Chou-Fasman algorithm (35) showed that the peptide comprising the first 20 amino acids was remarkably hydrophobic in character and that a second set of sequences (residues 50–100) was highly hydrophilic in character. The hydrophobic character of the lead peptide suggests that ACC2 may be a membrane-targeted or -bound enzyme. The association of ACC2 with cellular membranes (mitochondrial, nuclear, and endoplasmic) may reflect its function within the cell. At this time, however, the physiological significance of the 280-kDa ACC2 and its 270-kDa isoform is not clear. Nevertheless, all available evidence suggests a role for ACC2 in the regulation of fatty acid oxidation. The presence of ACC2 in nonlipogenic tissues such as heart and skeletal muscle, in which very little fatty acid synthesis occurs but in which there are very high levels of fatty acid oxidation, is presumed to catalyze the synthesis of malonyl-CoA, a potent inhibitor of the carnitine palmitoyltransferase 1 system and thereby to regulate mitochondrial fatty acid oxidation.

The heart derives its energy primarily from the oxidation of fatty acids and carbohydrates. The consumption and balance

**Fig. 4.** PCR amplification of cDNA fragments representing the putative 270- and 280-kDa human ACC2 isoforms. A, first-strand cDNA, synthesized from human liver mRNA, was used as a template in a PCR reaction that yielded two distinct DNA fragments that were separated by electrophoresis on a 1% agarose gel (lane 2). Lane 3, DNA products were transferred to a nitrocellulose membrane and subjected to Southern blot analysis. Lane 1 contains standard DNA molecular weight markers. The numbers on the left indicate the size of the markers in kb.

**Fig. 5.** Expression of ACC in various human and mouse tissues. Northern blot analysis of ACC2 mRNA performed on various human and mouse tissues. Each lane was loaded with 2 μg of poly(A)+ mRNA that was prepared from the indicated tissues. A, multiple human tissues; B, human muscle tissues; C, multiple mouse tissues. The blots were probed with a 32P-labeled 400-bp PCR fragment that corresponded to the N-terminal region of human ACC2. Hybridization was performed at 42 °C for 20 h in formamide hybridization buffer, and the blots were washed four times with 0.1 × SSC in 0.1% SDS at 55 °C. The numbers to the left of the blots represent standard molecular weight markers in kb. Lanes are as follows: H, heart; B, brain; P, placenta; L, lung; E, liver; Sm, skeletal muscle; K, kidney; Pa, pancreas; U, uterus (no endometrium); C, colon (no mucosa); St, small intestine; Bf, bladder; St, stomach; P, prostate; Sp, spleen; T, testis.
between the utility of the two substrates becomes important to the function of the heart. Since $\beta$-oxidation of fatty acids utilizes CoA as a substrate and yields acetyl-CoA as a product, as does the oxidation of pyruvate via the pyruvate dehydrogenase complex, the mitochondrial acetyl-CoA:CoA ratio becomes a factor in influencing the activities of the two pathways. $\beta$-Oxidation of fatty acids results in an increase in the acetyl-CoA:CoA ratio, leading to a decrease in the activity of the pyruvate dehydrogenase complex that then results in a decrease in carbohydrate oxidation (24, 36). Conversely, stimulating glucose oxidation by increasing the activity of the pyruvate dehydrogenase complex by, for example, dichloroacetate (37), leads to an increase in the acetyl-CoA:CoA ratio and a decrease in fatty acid oxidation by the mitochondria (38). These results could be explained by the inhibition of thiolase activity resulting from an increase in the intramitochondrial concentration of acetyl-CoA (39). However, the presence of ACC2 in heart and muscle tissues and the role of its product malonyl-CoA in regulating carnitine palmitoyltransferase 1 activity suggested a role for carnitine and ACC2 in regulating the oxidation of fatty acids and carbohydrates by heart and muscle. In this role, carnitine is a substrate of the carnitine palmitoyltransferase 1 system that shuttles long chain fatty acyl groups across the mitochondrial membrane. Carnitine also is involved in the export of acetyl-CoA from the mitochondria to the cytosol via the carnitine acetyltransferase. Thus, the presence of carnitine would decrease the intramitochondrial acetyl-CoA:CoA ratio by translocating the acetyl-CoA from the mitochondria to the cytosol, where it is converted by ACC2 into malonyl-CoA, a potent but reversible inhibitor of carnitine palmitoyltransferase 1 ($K_i = 50 \text{ nM}$ (40, 41)), and thereby decreasing the fatty acyl substrate available for $\beta$-oxidation. In this scheme, ACC2 and carnitine acetyltransferase are key players in the regulation of fatty acid and carbohydrate oxidation in the heart.

Alternatively, ACC2 may also be important in the heart and muscle by providing malonyl-CoA for the elongation of fatty acids into very long chain acids that are required for the structure of the cellular membrane. Another possibility is that malonyl-CoA is required for the synthesis of as yet unknown compounds (possibly a polyketide) or in a metabolic pathway that is needed for cell viability, much as ACC is essential for the growth and viability of yeast cells (4, 5) or, in the case of
fission yeast, in the structure-function of the nuclear membrane and division and separation of the nucleus (42, 43).

**Acknowledgments**—We thank the Molecular Biology Computational Resource at Baylor College of Medicine for providing access to the computer programs we used for the sequence analysis. We also thank Pamela Paradis Powell for editing the manuscript.

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J. Biol. Chem. 1997, 272:10669-10677.
doi: 10.1074/jbc.272.16.10669

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