Peroxisomal Fatty Acid Oxidation Is a Substantial Source of the Acetyl Moeity of Malonyl-CoA in Rat Heart

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Little is known about the sources of acetyl-CoA used for the synthesis of malonyl-CoA, a key regulator of mitochondrial fatty acid oxidation in the heart. In perfused rat hearts, we previously showed that malonyl-CoA is labeled from both carbohydrates and fatty acids. This study was aimed at assessing the mechanisms of incorporation of fatty acid carbons into malonyl-CoA. Rat hearts were perfused with glucose, lactate/pyruvate, and a fatty acid (palmitate, oleate or docosanoate). In each experiment, substrates were 13C-labeled to yield singly or/doubly labeled acetyl-CoA. The mass isotopomer distribution of malonyl-CoA was compared with that of the acetyl moiety of citrate, which reflects mitochondrial acetyl-CoA. In the presence of labeled glucose or lactate/pyruvate, the 13C labeling of malonyl-CoA was up to 2-fold lower than that of mitochondrial acetyl-CoA. However, in the presence of a fatty acid labeled in its first acetyl moiety, the 13C labeling of malonyl-CoA was up to 10-fold higher than that of mitochondrial acetyl-CoA. The labeling of malonyl-CoA and of the acetyl moiety of citrate is compatible with peroxisomal β-oxidation forming C12 and C14 acyl-CoA and contributing >50% of the fatty acid-derived acetyl groups that end up in malonyl-CoA. This fraction increases with the fatty acid chain length. By supplying acetyl-CoA for malonyl-CoA synthesis, peroxisomal β-oxidation may participate in the control of mitochondrial fatty acid oxidation in the heart. In addition, this pathway may supply some acyl groups used in protein acylation, which is increasingly recognized as an important regulatory mechanism for many biochemical processes.

Malonyl-CoA is an intermediate of fatty acid synthesis in lipogenic organs. It is also a key regulator of mitochondrial long-chain fatty acid oxidation in most mammalian tissues because it modulates the activity of carnitine palmitoyltransferase-I (1–4). Malonyl-CoA is formed by cytosolic acetyl-CoA carboxylase (ACC)5 and is disposed off either by lipogenesis or via malonyl-CoA decarboxylase, which reforms acetyl-CoA. Alterations in malonyl-CoA metabolism and regulation have been associated with insulin resistance and obesity (5). Mice lacking ACCβ, the predominant ACC isoform in cardiac and skeletal muscle, show not only decreased malonyl-CoA levels and increased fatty acid oxidation but also major alterations in systemic energy balance with decreased body fat despite increased food intake (6). The above data emphasize the crucial role of malonyl-CoA in fat metabolism and energy balance.

In the heart, much work has been conducted on the control of malonyl-CoA metabolism, emphasizing the mechanisms of regulation of ACCβ and malonyl-CoA decarboxylase. This includes acute changes in activity through phosphorylation via cAMP-dependent protein kinase or AMP kinase (for recent reviews, see Refs. 5 and 7–10), as well as chronic regulation through gene expression involving peroxisomal proliferator-activated receptor (11, 12). However, little is known about the origin of acetyl-CoA used for malonyl-CoA synthesis. Acetyl-CoA is produced predominantly in the mitochondria. The concentration of acetyl-CoA available to cytosolic ACCβ appears to be in the low μM range (13), i.e. much below the Km of ACCβ for acetyl-CoA. It has been proposed that mitochondrial acetyl-CoA is transferred to the cytosol either via acetyl carnitine and the carnitine acetyl transferase system (14) or via citrate and ATP-citrate lyase (15, 16). Arguing against the role of acetyl carnitine is the reported absence of extramitochondrial carnitine acetyl transferase in the heart (17). Although the activity of ATP-citrate lyase in the heart is low, it could sustain the rates of increase in malonyl-CoA concentration measured in perfused rat hearts following the addition of substrates that raise malonyl-CoA concentration (16). The physiological release of citrate by the heart (18, 19) implies that citrate is available to cytosolic ATP-citrate lyase after transport from the mitochondria (20). Using a new gas chromatography-mass spectrometry technique (21), we showed that [13C]oleate contributes carbon to the acetyl moiety of malonyl-CoA (16). Also, experiments with hydroxycitrate, an inhibitor of ATP-citrate lyase, support an at least partial role of citrate as a precursor of the acetyl moiety of malonyl-CoA in the heart (16) and in muscle (15).

The present study was undertaken to characterize the contributions of glucose, lactate/pyruvate, and fatty acids of different chain length to the acetyl moiety of malonyl-CoA in rat hearts perfused under conditions that mimic the in vivo milieu, in terms of substrate supply to the heart. We used mass isotopomer2 analysis (23) to compare the labeling patterns of malonyl-CoA and of the acetyl moiety of citrate labeled from various 13C-labeled substrates. Our strategy was to use combi-
nations of labeled substrates that generate M2 and M1 mitochondrial acetyl-CoA, for example, [U-13C3](lactate + pyruvate) and [1-13C]oleate, respectively. Our data clearly demonstrate the participation of peroxisomal β-oxidation (24–26) to the supply of acetyl-CoA to malonyl-CoA formation.

EXPERIMENTAL PROCEDURES

Materials—Chemicals and biochemicals were obtained from Sigma. [U-13C6]Citric acid, [1,2,3,4-13C4]Docosanoic acid was synthesized from stearyl bromide and ethyl [U-13C4]acetoacetate (Merck Sharp & Dohme). ATP-citrate lyase was prepared from the livers of rats (28) to the supply of acetyl-CoA to malonyl-CoA formation.

Carbon Sources of Malonyl-CoA in the Heart

In all groups, hearts from overnight-fasted rats were perfused with non-recirculating buffer containing 3% bovine serum albumin, 50 μM carnitine, 100 micromarts/ml insulin and unlabeled or labeled 4 or 5 mM glucose, 0.5 or 1 mM lactate, 0.1 or 0.2 mM pyruvate, and 0.1 to 0.4 mM fatty acid, as indicated. The last column shows the average labeling ratios (malonyl-CoA)/(acetyl moiety of citrate) for the M1 and M2 isotomers. The ratios are presented as means ± S.E. (n = 6 or 7), *p < 0.05, **p < 0.01, ***p < 0.001. NS, non significant using paired t test.

| Groups | [Glucose] | [Lactate] | [Pyruvate] | [Fatty acid] |
|--------|-----------|-----------|------------|-------------|
|        | mM        | mM        | mM         | mM          |
|        | [U-13C6]  | [U-13C6]  | [U-13C6]   | [U-13C6]    |
| 1      | 1         | 1         | 1          | 1           |
| 2      | 5 [U-13C6]C5 | 1         | 0.2 [U-13C5] | 0.3 [1-13C]oleate |
| 3      | 4         | 0.5       | 0.5        | 0.1 [1,2,3,4,13C4]docosanoate |
| 4      | 4         | 0.5       | 0.5        | 0.1 [1,2,3,4,13C4]palmitate + 0.2 palmitate |
| 5      | 4 [U-13C6] | 0.5 [3-13C] | 0.1 [3-13C] | 0.4 palmitate |
| 6      | 4         | 0.5       | 0.5        | 0.1 [16-13C]palmitate + 0.2 [1,2,3,4,13C4]palmitate |

Labeling ratio (malonyl-CoA)/(acetyl moiety of citrate) obtained for the perfusions conducted for various times under a given experimental condition are reported as means ± S.E. of n perfusion experiments.

RESULTS

Experiments with Oleate—In the first two series of experiments, hearts were perfused with buffer containing 5 mM glucose, 1.0 mM lactate, 0.2 mM pyruvate, and 0.3 mM oleate (Table I, Groups 1–2). An 13C substrates, we used [U-13C3]lactate + pyruvate plus [1-13C]oleate (Group 1) or [U-13C6]glucose (Group 2). In these cases, the M2 and M1 enrichments of malonyl-CoA reflect the contribution of carbohydrate and oleate oxidation, respectively, to the acetyl moiety of malonyl-CoA. Similar considerations apply to the labeling of the acetyl moiety of citrate, which reflects mitochondrial acetyl-CoA. For this and subsequent sections, the time courses of labeling of malonyl-CoA and the acetyl moiety of citrate are presented in Figs. 1–4. The M1 and M2 labeling ratios (malonyl-CoA)/(acetyl moiety of citrate) obtained in the last column of Table I.

The M2 enrichment of malonyl-CoA from [U-13C3]lactate +
pyruvate) (2.5–5%, Fig. 1A) and from [U-13C6]glucose (10%) reflected a low contribution of extra-cellular carbohydrates to malonyl-CoA. In contrast, the M1 enrichment of malonyl-CoA from [1-13C]oleate increased progressively without plateauing and reached about 19% after 45 min (Fig. 1A). This was unexpected because, in the presence of [1-13C]oleate, the maximal M1 enrichment of mitochondrial acetyl-CoA is 100/9 = 11%, assuming zero contribution from glucose and lactate/pyruvate to acetyl-CoA. Therefore, the 19% M1-labeled acetyl moiety of malonyl-CoA could not be derived solely from mitochondrial acetyl-CoA. Indeed, the M1 enrichment of the acetyl moiety of citrate plateaued at 9% (Fig. 1B). Thus [1-13C]oleate contributed 9 × 9 = 81% to mitochondrial acetyl-CoA. However, the M1 enrichment of the acetyl moiety of citrate (9%) was about one-half that of malonyl-CoA (19%). In contrast, the M2 enrichment of the acetyl moiety of citrate derived from [U-13C3](lactate + pyruvate) or [U-13C6]glucose plateaued at a value that was ~2-fold greater than that of malonyl-CoA (5 and 18%, respectively). The combined data of Groups 1 and 2 show that the contributions of exogenous oleate, lactate plus pyruvate, and glucose to mitochondrial acetyl-CoA, 81, 4, and 18%, respectively, add up to close to 100%. These results, which concur with previous ones (16, 19), indicate that there is little if any contribution of endogenous substrates to mitochondrial acetyl-CoA.

Taken together, the data of Fig. 1, A and B, demonstrate that some of the malonyl-CoA label derived from [1-13C]oleate does not arise from the mitochondrial metabolism of this substrate. To explain this finding, we hypothesized that the high M1 enrichment of malonyl-CoA was derived, in part, from the partial peroxisomal β-oxidation of [1-13C]oleate, forming highly enriched [1-13C]acetyl-CoA in the vicinity of ACC.

Experiments with Docosanoate—To provide support for a contribution of peroxisomal β-oxidation of fatty acids to malonyl-CoA formation, we used [1,2,3,4-13C4]docosanoate (Table I, Group 3). Docosanoate is a very long-chain C22 fatty acid that is partly oxidized in peroxisomes (25). Because of its low solubility, even in the presence of 3% bovine serum albumin, we perfused rat hearts with only 0.1 mM [1,2,3,4-13C4]docosanoate. Fig. 2 shows the high M2 labeling of malonyl-CoA, which peaked at about 43%. In contrast, the M2 enrichment of the acetyl moiety of citrate plateaued at only about 4%. Since only 2 of the 11 acetyl units of [1,2,3,4-13C4]docosanoate were labeled, complete mitochondrial oxidation of the substrate would have resulted in a maximal M2 enrichment of the acetyl moiety of citrate of 18%. In the presence of [1,2,3,4-13C4]docosanoate, the 10-fold difference in the M2 enrichments of malonyl-CoA and acetyl moiety of citrate strongly suggests that most of the acetyl moiety of malonyl-CoA is derived from peroxisomal β-oxidation.

Experiments with Palmitate—In the experiments reported in the above sections, the fatty acids oleate and docosanoate were 13C-labeled on the first acetyl. These tracers do not allow probing specifically the fate of the omega acetyl, which, presumably, forms acetyl-CoA only in mitochondria. The availability of differentially 13C-labeled palmitate, [U-13C16]-, [16-13C]-, or [1,2-13C]palmitate allowed us to probe the fates of the various acetyl groups of palmitate. For these sets of perfusions, hearts
were perfused with buffer containing 4 mM glucose, 0.5 mM lactate, 0.1 mM pyruvate, and 0.4 mM palmitate (Table I, Groups 4–6).

Let us first consider the two groups of perfusions conducted with 0.2 mM [U-13C16]palmitate + 0.2 mM unlabeled palmitate (Group 4) and with [U-13C6]glucose + [3-13C](lactate + pyruvate) + 0.4 mM unlabeled palmitate (Group 5). As shown in Fig. 3A, the M2 enrichment of malonyl-CoA labeled from 50% enriched [U-13C16]palmitate increased almost linearly to 27% at 35 min without plateauing. In the same experiments, the M2 enrichment of the acetyl moiety of citrate peaked at 37% at 30 min. Therefore, since [U-13C16]palmitate was 50% enriched, the contribution of 0.4 mM palmitate to mitochondrial acetyl-CoA peaked at 74%. In parallel experiments with [U-13C6]glucose + [3-13C](lactate + pyruvate) + unlabeled palmitate (Group 5), the M2 and M1 enrichments of malonyl-CoA plateaued at 22 and 6%, respectively (Fig. 3B). As in the experiments with oleate, the contributions of palmitate, lactate/pyruvate, and glucose to mitochondrial acetyl-CoA add up to close to 100%, indicating little contribution from endogenous sources.

Lastly, one group of perfusions was conducted under the same conditions with a mixture of [16-13C]palmitate and [1,2-13C2]palmitate (Group 6). These two 13C substrates allow probing in the same experiment the fates of the last and the first acetyl groups of palmitate, as M1 and M2 isotopomers, respectively. Hearts were perfused with 0.2 mM [16-13C]palmitate + 0.2 mM [1,2-13C2]palmitate, each tracer being thus 50% enriched (Table I, Group 6). As shown in Fig. 4, the M1 enrichment of malonyl-CoA was ~10-fold lower than its M2 enrichment. In contrast, the M1 enrichment of the acetyl moiety of citrate was 2-fold lower than its M2 enrichment. These data provide clear evidence for a differential metabolism of the α and ω acetyl groups of palmitate.

DISCUSSION

According to current concepts, the acetyl-CoA used by heart cytosolic acetyl-CoA carboxylase to form malonyl-CoA (i) is of mitochondrial origin and (ii) is transferred from the mitochondria via acetyl carnitine (14) or via citrate and ATP-citrate lyase (15, 16). The major finding of this study is the demonstration that a substantial proportion of malonyl-CoA is synthesized from acetyl-CoA molecules derived from extramitochondrial long-chain chain fatty acid β-oxidation. This was evidenced by comparing the [13C] labeling of malonyl-CoA with that of the acetyl moiety of citrate, which reflects mitochondrial acetyl-CoA. In the presence of fatty acids labeled in the first acetyl moiety, the labeling ratio (malonyl-CoA/acyt iscitrate) was greater than 1.0. In contrast, in the presence of labeled glucose or lactate/pyruvate, the labeling ratio (malonyl-CoA/acyt iscitrate) was smaller than 1.0.

In hearts perfused with [U-13C3](lactate + pyruvate) and [1-13C]oleate, the M2 enrichment of malonyl-CoA (from [U-13C3](lactate + pyruvate)) plateaued at about one-half that of mitochondrial acetyl-CoA (Fig. 1B). This implies that the labeling of M2 acetyl-CoA transferred from mitochondria was diluted by unlabeled acetyl-CoA formed in the extramitochondrial space. The only known source of unlabeled extramitochondrial acetyl-CoA (in the absence of exogenous acetate) is the partial peroxisomal oxidation of fatty acids. Although [1-13C]oleate was M1-labeled in its first acetyl, its oxidation did not generate any M2 acetyl-CoA. Therefore, all acetyl-CoA molecules derived from the partial peroxisomal oxidation of [1-13C]oleate are “M2 unlabeled” and dilute the M2 labeling of acetyl-CoA derived from [U-13C3](lactate + pyruvate). In contrast, the M1 enrichment of malonyl-CoA labeled from [1-13C]oleate was twice that of mitochondrial acetyl-CoA. The latter finding can only be explained by the formation of M1 acetyl-CoA molecules through extramitochondrial oxidation of [1-13C]oleate, most likely in peroxisomes.

In fact, it appears that, under the conditions of these experiments, about one-half of the extramitochondrial acetyl-CoA used to form malonyl-CoA was derived from the mitochondria, and one-half was derived from extramitochondrial β-oxidation of fatty acids. Since the M2 enrichment of mitochondrial acetyl-CoA derived from [U-13C3](lactate + pyruvate) was diluted 2-fold after its transfer to the extramitochondrial space, we can assume that a similar 2-fold dilution occurred to the M1 enrichment of mitochondrial acetyl-CoA derived from [1-13C]oleate (9% to 4.5%). Then, we can calculate the M1 enrichment of extramitochondrial acetyl-CoA derived from the partial peroxisomal β-oxidation of [1-13C]oleate. Out of 100 molecules of malonyl-CoA, 50 were derived from acetyl-CoA enriched at 4.5%, and 50 were derived from acetyl-CoA enriched at X%.

Fig. 3. Mass isotopomer distributions of (A) malonyl-CoA and (B) the acetyl moiety of citrate in hearts perfused with 50% enriched [U-13C16]palmitate or with [U-13C6]glucose + [3-13C](lactate + pyruvate) (Groups 4 and 5).
Solving a simple algebraic equation yields a 33.5% enrichment of acetyl-CoA derived from the peroxisomal β-oxidation of [1,13C]oleate. Since one in three acetyl units derived from peroxisomal β-oxidation was labeled, it appears that [1,13C]oleate underwent three cycles of peroxisomal oxidation, on average. This assumes that the exogenous [1-13C]oleate was the sole fuel of peroxisomal β-oxidation in these hearts. Our data are compatible with current concepts on partial peroxisomal β-oxidation of (very) long-chain acyl-CoAs (28). Presumably, [1-13C]oleate was degraded in peroxisomes to an unlabeled C12 CoA ester, which either was transferred to the mitochondria for further oxidation or alternatively could be involved in the acylation of heart proteins (30).

Additional evidence for the participation of an extramitochondrial β-oxidation pathway to the formation of acetyl-CoA for malonyl-CoA synthesis comes from perfusion experiments with [1,2,3,4-13C4]docosanoate. Under this condition, if the 40% enriched extramitochondrial acetyl-CoA were to be entirely degraded in peroxisomes to an unlabeled C12 CoA ester, the latter would have undergone five cycles of peroxisomal β-oxidation to form 40% enriched acetyl-CoA and unlabeled dodecanoyl-CoA. The presence of some labeling of mitochondrial acetyl-CoA can result from the transfer from the extramitochondrial to the mitochondrial space of (i) [1,2,3,4,13C4]docosanoyl-CoA or of [1,2,3,13C3,4-13C4]docosanoyl-CoA (derived from the former by one cycle of peroxisomal β-oxidation) via the carnitine palmitoyltransferase system or (ii) [1,2,13C3]acetyl-CoA derived from partial peroxisomal β-oxidation of [1,2,3,4,13C4]docosanoate, via the carnitine acetyltransferase system. The first mechanism is compatible with the presence of a very long-chain acyl-CoA dehydrogenase and a very long-chain trifunctional enzyme in mitochondria (31, 32).

In a third set of perfusion experiments (Group 6), an equimolar mixture of palmitate tracers labeled in the first (1,2,13C2)palmitate or last (16-13C)palmitate) acetyl units provided more insight into the mechanisms involved in the extramitochondrial formation of acetyl-CoA. The M1 enrichment of malonyl-CoA was lower than its M2 enrichment. This was expected since (i) [16-13C]palmitate would label malonyl-CoA only via labeling of mitochondrial acetyl-CoA, whereas (ii) [1,2,13C2]palmitate would label malonyl-CoA via mitochondrial acetyl-CoA and peroxisomal β-oxidation. Comparing the mass isotopomer distributions of the acetyl moiety of citrate and of malonyl-CoA in these hearts reveals that the M2 enrichment of malonyl-CoA, derived from [1,2,13C2]palmitate, is somewhat higher than the M2 enrichment of the acetyl moiety of citrate. Therefore, some of the M2 labeling of malonyl-CoA was probably derived from partial peroxisomal β-oxidation of [1,2,13C2]palmitate. Also, the M1 enrichment of malonyl-CoA, derived from [16-13C]palmitate, is lower than the M1 enrichment of the acetyl moiety of citrate. This probably results from the production of unlabeled acetyl-CoA by partial peroxisomal β-oxidation of [16-13C]palmitate. The degree of dilution of (M1 enrichment of acetyl moiety of citrate)/(M1 malonyl-CoA) is imprecise because of the low M1 enrichment of malonyl-CoA. If one estimates the dilution factor at about 2–3, using the rationale described for the experiments with [1-13C]oleate, one would conclude that the labeled substrate went through one or two cycles of peroxisomal β-oxidation. This is compatible with the estimate of Veerkamp and Van Moerkkerk’s (33), derived from incubations of rat heart homogenates with [1-13C]palmitate in the presence of antimycin and rotenone.

The interpretation of the difference in the M1 and M2 labelings of malonyl-CoA is somewhat complicated by the fact that the M2 labeling of the acetyl moiety of citrate from [1,2-13C2]palmitate was about twice that of its M1 labeling from [16-13C]palmitate (Fig. 3). One could have expected that the two tracers would equally label the acetyl moiety of citrate. This difference can be explained by the following considerations. The transfer of label from [16-13C]palmitate to mitochondrial acetyl-CoA is only partial because of the combined effects of (i) the incomplete isotopic equilibrium of the mitochondrial acetocacetyl-CoA thiolase reaction (34, 35) and (ii) the reversibility of the mitochondrial 3-oxoacid-CoA transferase reaction that converts acetocacetyl-CoA to acetocacetate (19, 35). In the reversible acetocacetyl-CoA thiolase reaction, the exchange of the C3+4 acetyl of acetocacetyl-CoA with the free acetyl-CoA pool is much slower than the exchange of the C1+2 acetyl (34). This was also observed in liver for the mitochondrial (34, 36, 37) and cytosolic acetocacetyl-CoA thiolase (38). Therefore, acetocacetyl-CoA derived from the last four carbons of [16-13C]palmitate is more labeled in its C3+4 acetyl compared with its C1+2 acetyl. Through the reversible 3-oxoacid-CoA transferase reaction, the asymmetrically labeled acetocacetyl-CoA is partly converted to asymmetrically labeled acetocacetate, which is released in the perfusate (35). As a
result, the mitochondrial acetyl-CoA pool is more labeled when palmitate is labeled in its first versus last acetyl moiety.

There are no precise estimates of the contribution of peroxisomal oxidation to the total rate of long-chain fatty acid oxidation in the heart (25). However, using data from this study, one can estimate the range of the rate of peroxisomal oxidation needed to sustain the production of malonyl-CoA. The turnover of rat heart malonyl-CoA is about 5 nmol/min/g of wet weight (21). Since peroxisomal oxidation contributes at least one-half of the acetyl-CoA used for malonyl-CoA synthesis, the latter could be supported by a rate of peroxisomal oxidation of about 2.5 nmol acetyl/min/g of wet weight (21). This rate is 100 times lower than the rate of acetyl-CoA produced from peroxisomal fatty acid oxidation can also be used in acetylation reactions. Also, the concentration of cytosolic acetyl-CoA is much lower than the mitochondrial acetyl-CoA pool is more labeled when palmitate is labeled in its first acetyl moiety.

Carbon Sources of Malonyl-CoA in the Heart

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