Malonyl-CoA, a Key Signaling Molecule in Mammalian Cells

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Abstract

Malonyl-CoA can be formed within the mitochondria, peroxisomes, and cytosol of mammalian cells. Besides being an intermediate in the pathways of de novo fatty acid biosynthesis and fatty acid elongation, malonyl-CoA has an important signaling function through its allosteric inhibition of carnitine palmitoyltransferase 1, the enzyme that normally exerts flux control over mitochondrial β-oxidation. Malonyl-CoA is rapidly turned over in mammalian cells, and the activities of acetyl-CoA carboxylase and malonyl-CoA decarboxylase are important determinants of its cytosolic concentration. It is now recognized that malonyl-CoA participates in a diverse range of physiological or pathological responses and systems. These include the ketogenic response of the liver to fasting and diabetes, carbohydrate versus fat fuel selection in muscle tissues, metabolic changes in muscle during contracture, alterations in fatty acid metabolism during cardiac ischemia and postischemic reperfusion, stimulation of B cell insulin secretion by glucose, and the hypothalamic control of appetite.

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INTRODUCTION AND BRIEF HISTORICAL BACKGROUND

It seems appropriate to review this topic in 2008 since this year marks half a century since the pioneering studies of Wakil and colleagues discovered that a malonic acid derivative, which was subsequently shown to be malonyl-CoA and the product of the acetyl-CoA carboxylase (ACC) reaction, was an intermediate in mammalian fatty acid biosynthesis (reviewed in 132). Our early perception that malonyl-CoA was nothing more than a metabolic intermediate, albeit in an important biosynthetic pathway, underwent a major change in the late 1970s, largely because of the work of McGarry and colleagues (see 86 for a review). These investigators had set out to explain how the metabolic profile of the liver could be acutely switched from one that favored fatty acid esterification to one that favored fatty acid oxidation and ketogenesis following acute removal of insulin or the elevation of glucagon concentration and, longer term, in fasting and diabetes. The mitochondrial carnitine palmitoyltransferase (CPT) system consisting of an overt carnitine palmitoyltransferase (CPT1), a carnitine:acylcarnitine exchange carrier, and a latent carnitine palmitoyltransferase (CPT2) became implicated because fasting and diabetes only enhanced ketogenesis from fatty acids that accessed β-oxidation in the mitochondrial matrix through the CPT system. Also, when the oxidation of oleate by livers from fasted or diabetic rats was inhibited by (+)decanoylcarnitine (an inhibitor of the CPT system), metabolism of the fatty acid was redirected into esterification to triacylglycerol, and the prior ketogenic profile of the liver was abolished. A search began for a metabolic regulator of the CPT system, and eventually malonyl-CoA was shown

ACC: acetyl-CoA carboxylase

CPT: carnitine palmitoyltransferase

to be a potent inhibitor of CPT1 at concentrations typical of those measured in rat liver ($K_{0.5}$ of 1–2 μM). This led to the concept that the rates of hepatic fatty acid synthesis and β-oxidation/ketogenesis were inversely related with malonyl-CoA, the metabolic product of the highly regulated ACC reaction, providing the key link. This work established malonyl-CoA as a signaling molecule as well as a metabolic intermediate in a lipogenic tissue. Although the early 1980s saw the demonstration that nonlipogenic tissues such as heart and skeletal muscle contained measurable amounts of malonyl-CoA (87) and that CPT1 in mitochondria from many extrahepatic tissues was inhibitable by malonyl-CoA (112), these findings had little impact until it was discovered in the late 1980s and early 1990s that many tissues expressed ACC activity and hence had the ability to manufacture malonyl-CoA. A better understanding of malonyl-CoA decarboxylase (MCD) emerged during the late 1990s and early 2000s, with insight into how cytosolic malonyl-CoA could be turned over within nonlipogenic cell types, where malonyl-CoA functioned solely as a signaling metabolite to regulate CPT1. The discovery in the late 1980s of the adenosine monophosphate-activated protein kinase (AMPK), which acutely down-regulates ACC activity in many cell types, provided a further important expansion of our conceptual framework and led investigators to think in terms of an AMPK/ACC/malonyl-CoA/CPT1 regulatory axis.

MALONYL-CoA METABOLISM IN MAMMALIAN CELLS

The main reactions of malonyl-CoA metabolism are summarized in **Figure 1**. The cytosolic pool of malonyl-CoA that is relevant to the regulation of CPT1 is the product of the reaction catalyzed by the biotin-dependent enzyme ACC.

$$\text{acetyl-CoA} + \text{ATP} + \text{HCO}_3^- \rightarrow \text{malonyl-CoA} + \text{ADP} + P_i$$

Pools of malonyl-CoA are also presumed to exist within the mitochondrial matrix, generated by the adventitious activity of propionyl-CoA carboxylase on acetyl-CoA, and within peroxisomes from the β-oxidation of odd chain-length dicarboxylic acids. Early studies, which even predate the discovery of ACC, had suggested that malonyl-CoA could be formed from malonate that is present in some mammalian tissues (90), although the physiological significance of this unclear. There are three known routes for the disposal of malonyl-CoA. In lipogenic tissues such as liver, adipose tissue, and lactating mammary gland, malonyl-CoA is a cosubstrate for the condensation reaction of the cytosolic fatty acid synthase (FAS) complex, which drives the de novo synthesis of palmitate. Malonyl-CoA is also a cosubstrate for the fatty acid elongation system that is localized to the endoplasmic reticulum membrane (see 20 for a review). This system functions to chain lengthen both endogenously synthesized and dietary-derived fatty acids (for example, it transforms essential fatty acids into higher polyunsaturated fatty acids), and it plays an important specialized role in the formation in the CNS of C22 and C24 chain-length fatty acids during myelination. The third route of disposal is through the conversion of malonyl-CoA to acetyl-CoA that is catalyzed by MCD.

$$\text{malonyl-CoA} + \text{H}^+ \rightarrow \text{acetyl-CoA} + \text{CO}_2$$

MCD provides a route for the disposal of any malonyl-CoA that is formed within mitochondria and peroxisomes. There is no known route by which malonyl-CoA can escape from these organelles, and a deleterious pileup of malonyl-CoA could ensue without MCD. Within the cytosol, MCD and ACC appear to work in concert to control the pool of malonyl-CoA that regulates CPT1.

MEASUREMENT OF MALONYL-CoA

Malonyl-CoA is a hydrophilic metabolite and is readily extracted from freeze-stopped tissue with perchloric acid or trichloroacetic acid.

MCD: malonyl-CoA decarboxylase

AMPK: adenosine 5′-monophosphate-activated protein kinase

FAS: fatty acid synthase

MOM: mitochondrial outer membrane

Malonyl-CoA was first assayed spectrophotometrically by following reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase formation by FAS (53). This was converted into a radiochemical assay (88), which measured the malonyl-CoA dependent incorporation of [^{14}C]acetyl-CoA into fatty acid by FAS and that was more sensitive and amenable to assay of multiple samples. This assay, with or without minor modifications (5, 127), has been widely used. Malonyl-CoA can also be assayed in tissue extracts by reversed-phase high-performance liquid chromatography (75) or by first separating malonyl-CoA from other short-chain acyl-CoA thioesters followed by alkaline hydrolysis and quantitation of the resulting malonate by gas chromatography–mass spectrometry (103). Measurements of malonyl-CoA in normal mammalian cells and tissues are generally within the range of 1–15 nmol per g wet weight, which translates into intracellular concentrations in the low micromolar range. It should be noted that these are global cellular concentrations. No method has yet been devised that can determine the cytosolic concentration of malonyl-CoA or the concentrations within organelles such as mitochondria, peroxisomes, and nuclei.

REGULATION OF ACETYL-CoA CARBOXYLASE, MALONYL-CoA DECARBOXYLASE, AND THE CONTROL OF MALONYL-CoA CONCENTRATION

General Comments

The opposing activities of ACC and MCD provide for an acetyl-CoA/malonyl-CoA cycle and appear to be important determinants in dynamically setting the size of the cellular pool(s) of malonyl-CoA. The combined activities of ACC and MCD result in a rapid turnover of malonyl-CoA. The half-lives for labeling and delabeling of malonyl-CoA with [^{13}C]bicarbonate are less than 20 seconds in perfused rat liver and are 1.4 and 1.1 minutes, respectively, in perfused rat heart (103). The published range of values of the K_m of MCD for malonyl-CoA (42–250 μM) are at least an order of magnitude higher than the levels of malonyl-CoA in tissues, and therefore the turnover of malonyl-CoA is linearly correlated with the malonyl-CoA content (104). Likewise, at least in the heart, the concentration of cytosolic acetyl-CoA is suggested to be much lower than the K_m of ACC for acetyl-CoA (110).

The Expression and Regulation of the Isoforms of Acetyl-CoA Carboxylase

Mammalian ACC is expressed as two proteins, termed ACC 265, ACC-1, or ACC-α and ACC 280, ACC-2, or ACC-β. ACC-α is thought to function more, but not exclusively, as a provider of malonyl-CoA for lipogenesis, whereas ACC-β is thought to function primarily as a source of malonyl-CoA to regulate CPT1 and control mitochondrial β-oxidation. ACC-α is essential for embryonic development in mice (3). It is the most abundant form of ACC protein in lipogenic tissues such as liver, white adipose tissue, and mammary gland (9, 65) but is also found in other tissues such as heart (110, 128) and pancreatic islets (83). ACC-β protein is most abundantly expressed in skeletal muscle and heart (9, 65, 110, 128) but is also found in brown adipose tissue, mammary gland, and pancreatic islets (9, 83). Knockout of the ACCβ gene results in a nonlethal phenotype in which animals have increased β-oxidation in liver and muscle, are lean, and are hyperphagic. They are resistant to obesity and diet-induced diabetes. In muscle, they have a decreased malonyl-CoA content whereas hepatic malonyl-CoA is unchanged (2, 4). Compared with ACC-α, ACC-β has approximately 140 extra amino acid residues at its N-terminus, which contains a motif that allows targeting and/or binding to the mitochondrial outer membrane (MOM) (1). It is suggested that this could permit control of the malonyl-CoA concentration near the malonyl-CoA binding site of CPT1 (73). However, association of ACC-β with mitochondrial fractions extracted from tissues has been difficult to demonstrate. ACC-α and ACC-β are

acutely regulated by interacting allosteric and protein phosphorylation mechanisms, which are summarized in **Figure 2** (for reviews, see 7, 19, 56, 73, 74, 92). Long-chain fatty acyl-CoA thioesters allosterically inhibit ACC, an effect that is important in fasting and diabetes when plasma NEFA and hence cellular fatty acyl-CoAs are increased. Citrate is an allosteric activator that also prevents binding of fatty acyl-CoAs to ACC. Malonyl-CoA competitively inhibits ACC and therefore may act to self-limit its own production. ACC-α contains several potential serine phosphorylation sites. Those phosphorylated by protein kinase A (PKA) (Ser1200) and AMPK (Ser79) produce inactivation of ACC in vivo. AMPK and PKA both increase the K_a for citrate. However, while AMPK causes a 80%–90% decrease in the V_{max} of ACC-α, PKA causes only a modest (<15%) decrease in V_{max}. The major AMPK phosphorylation site (Ser79) in rat ACC-α is conserved in ACC-β as Ser218, and its phosphorylation again causes a decrease in V_{max} and an increase in the K_a for citrate. ACC-β is a good substrate for phosphorylation at multiple sites, which have yet to be defined but which may be particularly concentrated within the N-terminal extension and might regulate association of ACC-β with the MOM (73). Nutritional and hormonal control of ACC gene expression occurs, although the half-life of ACC protein(s) is quite long. For example, ACC expression is decreased in liver and white adipose tissue by fasting and diabetes and is restored by refeeding (96, 141), but these manipulations have no appreciable effect on ACC expression in muscle tissues (121, 134). Detailed reviews of the expression of ACC genes are available elsewhere (7, 73).

The Subcellular Distribution and Regulation of Malonyl-CoA Decarboxylase

That MCD has an important metabolic role is illustrated by malonic aciduria, an inborn error of metabolism in which MCD activity is deficient. This is characterized by cardiomyopathy, mental retardation, hypoglycemia, and episodes of organic aciduria. A single MCD mRNA is expressed; it is present in a range of adult rat tissues and is expressed at particularly high levels in liver, heart, and adipose tissue (131). Human MCD mRNA is strongly expressed in heart and skeletal muscle, and appreciable expression is also seen in liver, kidney, and pancreas (109). The highest expression of rat MCD protein is in liver and heart; appreciable expression is in skeletal muscle, kidney, lung, pancreas, and brain (31). MCD enzymatic activity can be detected across a range of rat tissues, with the greatest activities seen in the highly oxidative liver and heart tissues (131). In muscles, MCD activity correlates with oxidative capacity, being highest in cardiac muscle, lowest in type IIb fibers, and intermediate in types I and IIa fibers (71). Defining the subcellular targeting and localization of MCD has proved to be challenging; the task has been complicated by the existence of multiple forms of MCD protein. Early subcellular fractionation studies with rat liver concluded that MCD was confined to the mitochondrial matrix and therefore could not access the cytosolic pool of malonyl-CoA. Subsequent fractionation techniques have revealed the expression of MCD protein and activity in liver peroxisomal and cytosolic fractions as well as in mitochondria (68, 109).

The existence of a cytosolic as well as a mitochondrial MCD activity in types I, IIa, and IIb skeletal muscles has been shown (5, 71). In rat heart, MCD activity was observed in a crude mitochondrial fraction but no evidence was found for a cytosolic MCD (55). By contrast, the presence of cytosolic MCD activity in heart was reported (71). Both of these studies (55, 71), as well as a third study (30), reported the existence of overt mitochondrial MCD activity, which is between 16% and 23% of the total heart mitochondrial MCD activity and which ought to the accessible to cytosolic malonyl-CoA. The question of how and where this overt MCD is attached to heart mitochondrial membrane lipids or to membrane proteins remains unresolved. The open reading frame of rat MCD contains an N-terminal mitochondrial

PKA: 3′,5′-cyclic adenosine monophosphate-dependent protein kinase

AICAR: 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside

PKC: protein kinase C

targeting sequence and a C-terminal peroxisomal targeting motif (Ser-Lys-Leu). MCD protein in rat tissues (31) or overexpressed in H9c2 cells (123) has been found as a cytosolic long (54.7 kDa) form and as a mitochondrial short (50.7 kDa) form. Additionally, a 48–49 kDa form has been found in peroxisomes (68). Intuitively, one might expect the proportion of the cell MCD activity that can access the cytosolic pool of malonyl-CoA to be acutely regulated. In particular, it has been hypothesized that protein kinases that inactivate ACC might activate MCD. Some in vivo studies certainly support the notion that MCD is subject to regulation that is too rapid to be ascribed to transcription or protein translation. Brief contractile work resulted in a 55% increase in MCD activity in rat heart (50). MCD activity was increased in type IIa skeletal muscle by the AMPK activator AICAR, and brief electrical stimulation increased V_{max} and decreased the K_m for malonyl-CoA of MCD in type IIb muscle (119). Brief treadmill running increased MCD activity together with phosphorylation/deactivation of ACC in type IIb muscle, liver, and white adipose tissue (98). By contrast, no change was observed in MCD activity in an islet cell line following acute activation of AMPK or in fast twitch muscle following stimulation of contraction (although phosphorylation of ACC was seen) (54).

Studies in vitro have also yielded conflicting results. Rat MCD contains seven possible phosphorylation sites for CKII and three for PKC (131). MCD activity in heart and liver homogenates was increased by treatment with alkaline phosphatase (30, 31), which suggests that MCD might be inactivated by one or more protein kinase. However, phosphoprotein phosphatase 2A decreased MCD activity in muscle extracts (119) and the broad spectrum λ phosphatase had no effect on MCD activity (54). AMPK, PKA, PKC, and CKII had no effect on purified MCD (31), and no evidence was found for phosphorylation of MCD by AMPK (54, 123). By contrast, it was reported that AMPK, PKA, and CKII increased MCD in muscle immunoprecipitates (98). It is possible that these conflicting findings reflect methodological problems. Tissue freeze-stopping, which is necessary to preserve changes in protein phosphorylation, disrupts organelle architecture, and subsequent extracts therefore contain MCD derived from multiple compartments. Also, assays of MCD activity in crude extracts can be affected by interfering reactions. In order to minimize these reactions, MCD is often semipurified from crude homogenates before assay. It not known to what extent these treatments might affect experimental measurements. Further work is necessary to provide a clearer understanding of the acute regulation of MCD. MCD expression is also subject to longer-term regulation through changes in transcription or protein translation. Liver (31) and heart (121) MCD protein abundance and activity are increased by streptozotocin-diabetes, which also increases MCD mRNA in heart and types I and IIa muscles (136). Fasting also increases MCD mRNA, protein, and activity in these tissues (31, 136), and muscle and heart MCD mRNA is increased by fat feeding (136).

CARNITINE PALMITOYLTRANSFERASE ISOFORMS—THE PHYSIOLOGICAL SIGNALING TARGETS OF MALONYL-CoA

In the physiological direction, CPT1 catalyzes the following reaction:

$$\text{Fatty acyl-CoA} + \text{L-carnitine} \rightarrow \text{fatty acylcarnitine} + \text{CoASH}.$$

Mammalian cells express three isoforms, CPT1A, CPT1B, and CPT1C, which are encoded by three different genes (85, 101). CPT1A (L-type CPT1) is the sole or primary isoform in adult liver, lung, spleen, intestine, ovary, and pancreas. The heart also expresses CPT1A in the late fetal and neonatal rat, but this is largely replaced by CPT1B during later development (18). CPT1B (M-type CPT1) predominates in skeletal muscle, adult heart, brown and white adipocytes, and in testes. A CPT1 with kinetic properties similar to CPT1B

is present in fetal liver but is rapidly replaced by CPT1A postnatally (116, 129). Brain shows a complex pattern of CPT1 expression. mRNAs encoding CPT1A and CPT1C are found in many brain regions (79) as also is an enzyme activity with CPT1A-type kinetics (10). In addition, there is a high, unique expression of CPT1B mRNA in the cerebellum (79). Although the CPT1C protein has been expressed in *Pichia pastoris* in a form that binds malonyl-CoA with high affinity, it has no enzymic activity against any species of fatty acyl-CoAs that are known to be CPT1 substrates (101, 135). The function of CPT1C remains unknown at present. CPT1A is an integral protein of the MOM, with the enzyme abundance being enriched at mitochondrial contact sites as well as being found in "bulk" MOM (42). The topological features of CPT1A in the liver MOM have been defined (40), and these are highly relevant to the enzyme's physiological function and regulation by malonyl-CoA. Most of liver CPT1A is oriented toward the cytosolic side of the MOM as a ~46 amino acid N-terminal domain and a ~650 amino acid C-terminal catalytic domain. These are connected by two transmembrane segments linked by a short 27 amino acid residue hairpin loop that dips into the mitochondrial intermembrane space. The kinetics of CPT1A in situ in liver mitochondria or purified MOM fractions are complex. Malonyl-CoA increases the $K_{0.5}$ for the fatty acyl-CoA substrate, whereas fatty acyl-CoA attenuates both inhibition by malonyl-CoA (113) and high-affinity binding of malonyl-CoA to a MOM fraction (76). Malonyl-CoA also decreases the effectiveness of L-carnitine as a substrate while L-carnitine decreases the effectiveness of malonyl-CoA as an inhibitor (12). Inhibition involves the binding of malonyl-CoA at two sites within the catalytic domain. One is a low-affinity site through which malonyl-CoA competes against the fatty acyl-CoA site, whereas the second, high-affinity site shows no interaction with fatty acyl-CoA (11, 125, 126, 139). However, both malonyl-CoA sites share the same L-carnitine-binding locus (82). Although the N-terminal domain does not contain a malonyl-CoA binding site, it contains both positive and negative determinants of malonyl-CoA sensitivity (66, 67) and is essential for maintaining the integrity of the high-affinity malonyl-CoA binding site (124). Changes in sensitivity of liver CPT1A to malonyl-CoA correlate with changes in the molecular order of the membrane lipid core (140). Desensitization to malonyl-CoA (which also occurs in fasting and diabetes, as discussed below) results when increased temperature or benzyl alcohol increases the fluidity of the membrane (77, 140). Chemical cross-linking studies have shown that physiologically or chemically induced desensitization is due to alterations in the interaction between the N- and C-terminal domains (34). The amino acid sequence spanning the boundary between the intermembrane space loop and the more C-terminal of the transmembrane segments is also important in determining malonyl-CoA sensitivity (14). The importance of membrane environment is also evidenced by the finding that malonyl-CoA is a competitive inhibitor with respect to fatty acyl-CoA for liver mitochondrial contact site CPT1A, whereas it is noncompetitive in the bulk MOM CPT1A (41). Chemical cross-linking experiments have shown that liver CPT1A forms an oligomeric complex (35). This oligomeric structure is not at variance with the allosteric type of kinetics that the enzyme shows in response to malonyl-CoA. For example, inhibition by malonyl-CoA shows a hysteresis (23, 80, 138), and malonyl-CoA induces sigmoidicity into the relationship between fatty acyl-CoA and CPT1 activity (24, 111).

Liver microsomal and peroxisomal fractions also contain membrane-bound, malonyl-CoA-inhibitable CPT1 activities. These are very similar to mitochondrial CPT1A in their subunit size, immunological reactivity, and dependence of malonyl-CoA sensitivity on membrane environment (16, 17, 39). The lumen of the hepatic endoplasmic reticulum (ER) and the peroxisomal matrix contain latent, malonyl-CoA-insensitive CPT activities. Also, both the ER membrane and the peroxisomal

membrane have the capability to transport fatty acylcarnitine and L-carnitine (43, 49). Therefore, it has been suggested that liver CPT1A might be targeted to become an integral protein of both the ER and the peroxisomal membrane and thereby be part of a system for the transport of long-chain fatty acyl moieties into these organelles that is similar to the CPT1/CPT2 system of the mitochondria. However, no evidence was found for authentic insertion of CPT1A into ER membranes (16), and based on comparisons of CPT1 kinetics and porin distribution, it was proposed that the malonyl-CoA-inhibitable CPT1 in liver microsomal fractions is derived from mitochondrial contact sites. This would imply that if malonyl-CoA plays any role in regulating the transport of long-chain fatty acyl moieties into the ER lumen (for example, for biosynthesis of VLDL triacylglycerol or cholesteryl ester), the role must be at the level of mitochondrial CPT1 rather than through a specialized ER-targeted CPT1. Whether transport of long-chain fatty acyl moieties into peroxisomes could be directly regulated by malonyl-CoA through a peroxisome-targeted CPT1 remains to be established.

CPT1A and CPT1B have 62% predicted amino acid sequence identity overall and are presumed to have the same general structure and membrane topology. However, when assayed in isolated mitochondria, CPT1B has a nearly 100-fold lower IC_{50} for malonyl-CoA and a ~15-fold higher K_m for L-carnitine than CPT1A (87, 112). These two CPT1s also differ markedly in their hysteretic behavior with respect to malonyl-CoA (80). Studies with chimeric enzymes have shown that the presence of a CPT1B catalytic domain is required for high sensitivity to malonyl-CoA (66). Also, notable amino acid sequence differences exist between the two transmembrane segments of CPT1A and CPT1B, which are predicted to make CPT1B a more rigid structure that is much more resistant to changes in membrane lipid molecular order (66). In tissues that exclusively or predominantly express CPT1B, such as skeletal muscle and heart, the total tissue concentration of malonyl-CoA is 10- to 100-fold higher than the IC_{50} for inhibition of CPT1B by malonyl-CoA. This has posed a conceptual problem, leading to several suggestions as to how CPT1B could have any uninhibited activity and even how β-oxidation could happen at all in these tissues. The likelihood that some malonyl-CoA is within mitochondria or other organelles almost certainly means that total tissue measurements of malonyl-CoA do not reflect the cytosolic concentration that is available to inhibit CPT1. However, as discussed above, nobody has yet found a way to address this problem. Rat heart mitochondria contain a high-affinity binding site for malonyl-CoA (B_{MAX} = 7 pmol.mg^{-1}), which is likely to be CPT1 because inhibition of CPT1 correlates extremely well with its occupation (11). However, heart mitochondria additionally contain a much greater abundance of a low-affinity site (B_{MAX} = ~660 pmol.mg^{-1}), which is unrelated to CPT1 and that could sequester an appreciable amount of malonyl-CoA. In perfused rat hindlimb, a 50% inhibition of β-oxidation occurs at a tissue malonyl-CoA concentration of 0.6 nmol.g^{-1} (134), which is 18 times greater than the IC_{50} for inhibition of muscle mitochondrial CPT1 by malonyl-CoA (87), suggesting that an appreciable amount of cellular malonyl-CoA must be sequestered. Another answer to this conundrum has been suggested by Eaton and colleagues (33). Whereas in hepatocytes CPT1A has a very high flux control coefficient for β-oxidation (28), in heart mitochondria there appears to be considerable spare capacity of CPT1. This is reflected in CPT1 having a very low flux control coefficient for β-oxidation (0.08), with 50% of CPT1 activity able to be pharmacologically inhibited before β-oxidation is affected. Much of this spare capacity could be permanently inhibited by malonyl-CoA, leaving the remainder of the cell CPT1 activity, and hence β-oxidation, to be sensitive to different degrees of inhibition brought about by changes in malonyl-CoA concentration. Finally, heart and skeletal muscle express mRNAs for splicing isoforms of CPT1B, which are suggested to code for CPT1 enzymes that are insensitive to malonyl-CoA

and therefore could allow some β-oxidation to occur even at high malonyl-CoA concentrations (137). In support of this conjecture, both heart (89) and skeletal muscle (72) mitochondria express some malonyl-CoA-insensitive CPT1 activity. It seems reasonable to expect that some combination of the above processes is necessary to keep muscle β-oxidation running and regulated under physiological conditions, but it remains a mystery why CPT1B should be so exquisitely (and apparently unnecessarily) sensitive to malonyl-CoA.

THE AMPK/ACC/MALONYL-CoA/ CPT1 AXIS IN OPERATION IN PHYSIOLOGICAL AND PATHOLOGICAL SITUATIONS

A small number of organ-specific examples that particularly illustrate the role of malonyl-CoA are discussed below (a full account is beyond the scope of this review).

The Role of Malonyl-CoA in the Ketogenic Response of the Liver During Fasting and Diabetes

During transition from the fed to the fasted state, the direction of hepatic fatty acid metabolism is dramatically switched away from de novo fatty acid synthesis and toward β-oxidation and ketogenesis. Refeeding reverses this switch. A similar switch toward β-oxidation and ketogenesis is seen during the onset of insulin-dependent diabetes. In vivo hepatic malonyl-CoA levels in fasted or diabetic rats are approximately half of those in normal ad libitum–fed animals (8–13 nmol.g^{-1}) (53, 88), whereas meal feeding leads to a malonyl-CoA content that is twice the normal level. Likewise, decreases in hepatic malonyl-CoA of as much as 80%–85% have been observed after 24 hours of fasting of euthyroid rats (84); decreases of this scale were also seen in hyperthyroid rats as well as in hypothyroid animals, where the thyroid hormone–deficient state itself resulted in a twofold increase in malonyl-CoA in the fed state. Under euglycemic clamp conditions, insulin is able to reverse the fasting-induced decrease in hepatic malonyl-CoA (100). In isolated hepatocytes, glucagon decreased malonyl-CoA content by 55% within five minutes (26), and the long-chain fatty acid oleate also acutely decreased malonyl-CoA content in a manner that was additive to the effect of glucagon (25). In a series of studies with hepatocytes from meal-fed rats (summarized in 86), it was shown that rates of fatty acid synthesis and β-oxidation that could be acutely manipulated over a wide range were closely positively and negatively correlated, respectively, with the malonyl-CoA content. Acute down-regulation of ACC, in response to increases in the levels of glucagon and plasma long-chain fatty acids and a fall in insulin, is considered to be an important driver of the changes in hepatic malonyl-CoA that are seen in fasting and diabetes. The extent to which MCD may also play a part cannot be fully evaluated at present. Glucagon decreases ACC activity in hepatocytes, and phosphorylation of ACC-α Ser79 by AMPK appears to be the main way in which this is achieved (57). An increase in plasma fatty acid results in an increase in the hepatic content of long-chain fatty acyl-CoA with ensuing allosteric inhibition of ACC (**Figure 2**). Insulin causes acute activation of ACC, but the mechanism is unresolved. Activation of ACC through phosphorylation by an unidentified insulin-activated "ACC kinase" has been proposed (59). Activation of ACC secondary to inactivation of AMPK by insulin is an alternative possibility (93).

In fasting and ketotic diabetes, hepatic CPT1A becomes appreciably less sensitive to malonyl-CoA, as evidenced by a severalfold increase in the IC_{50} for inhibition of the enzyme by malonyl-CoA. This is seen when CPT1 is assayed in isolated mitochondria (15, 114) or with mitochondria in situ in selectively permeabilized hepatocytes (13) and is the result of an increase in the apparent K_i of the enzyme for malonyl-CoA (22, 46, 97). This desensitization to malonyl-CoA is slower in onset than the fall in malonyl-CoA content that occurs in fasting and diabetes (29, 52) and cannot be mimicked by an acute 30-minute exposure of perfused liver to glucagon (117). However, it occurs

more rapidly than increases in CPT1A protein that are dependent upon increased mRNA expression. On reversal of fasting or diabetes by refeeding or insulin, respectively, full resensitization of CPT1A to malonyl-CoA is achieved within 24 hours (51, 52). These changes in sensitivity to malonyl-CoA of CPT1A make a highly significant contribution to the ketogenic response of the liver and its reversal and serve to amplify the effects of faster changes in the cytosolic malonyl-CoA content. Since these sensitivity changes parallel changes in the apparent K_i for malonyl-CoA, parallel changes in the affinity of binding would be expected. Both fasting and diabetes were found to increase the K_D for binding of malonyl-CoA to a purified liver MOM fraction in a manner that closely correlated with increases in the IC_{50} for inhibition of CPT1 by malonyl-CoA (48). It seems likely that this high-affinity binding was actually to CPT1 because the B_{MAX} for this site and the V_{max} of CPT1 showed parallel three- to fourfold increases in diabetes and fasting. Yet it is perplexing that the K_D values measured by Ghadiminejad & Saggerson (48) were in the nM range, whereas apparent K_i values determined by others (22, 46) were in the μM range. Other studies of the binding of malonyl-CoA to liver mitochondria (11) or to a purified MOM fraction (76) did not show any effect of fasting upon a computed high-affinity K_D for malonyl-CoA. However, malonyl-CoA binding studies with whole mitochondria are likely to be complicated by the presence of many binding sites that are unconnected to CPT1. Differences between results of binding studies with MOM fractions (48, 76) can be attributed to differences in experimental conditions (47). We still do not fully understand the mechanisms that underlie these changes in sensitivity to malonyl-CoA. However, measurement of the fluorescence polarization index after the probe 1,6-diphenyl-1,3,5-hexatriene was introduced into hepatic MOM fractions indicated that fasting and diabetes had led to an increase in the fluidity of the lipid core of the membrane (140). As discussed above, this would be expected to loosen the rather flexible interaction between the N- and C-terminal domains of CPT1A, with a resulting modification in the properties of the malonyl-CoA binding site(s). Chemical cross-linking studies have suggested that this is the case in fasting and diabetes (34). Other studies support the notion that physiological changes in the sensitivity of CPT1A to malonyl-CoA result from changes in its membrane environment. Addition of cardiolipin to liver mitochondria from fasted rats increased the malonyl-CoA sensitivity to that found with mitochondria from fed animals (94), and decreasing the temperature for assay of CPT1A in MOM fractions abolished the fasting-induced desensitization to malonyl-CoA (47). The CPT1A activity found in hepatic microsomal fractions also shows desensitization to malonyl-CoA after fasting. When partially purified CPT1A from fed rats was reconstituted into liposomes prepared from microsomal membrane lipids from fed animals, it was more sensitive to malonyl-CoA than when reconstituted with liposomes prepared from membrane lipids from fasted animals (17).

The question of whether CPT1A kinetic properties might also be modified by direct phosphorylation of the enzyme has long been a matter of conjecture, but the finding that the C-terminus of CPT1A contains two phosphorylation sites for protein kinase CKII (70) is the only study that bears on this topic. Phosphorylation by CKII increased the V_{max} and changed malonyl-CoA inhibition from competitive to uncompetitive. The physiological significance of this effect is unclear. Changes in sensitivity of hepatic CPT1A to malonyl-CoA are not limited to fasting and diabetes but are also seen in other physiological states; discussion of these is beyond the scope of this review. The question of whether CPT1A in mitochondria of extrahepatic tissues might show similar reversible desensitization to malonyl-CoA does not appear to have been widely addressed, although fasting had no effect upon the malonyl-CoA sensitivity of rat brain CPT1A (10). In heart (22, 95, 99), skeletal muscle (130), and white adipocytes (115), there is no detectable desensitization of CPT1B to malonyl-CoA with fasting.

The Role of Malonyl-CoA in Balancing Cardiac Fuel Usage, and Disturbance of This Balance During Ischemic Reperfusion

Under normal physiological circumstances, the ATP that drives cardiac function is mainly derived from the aerobic catabolism of fatty acids, glucose, and lactate, with oxidation of fatty acids normally providing 50%–80% of this energy supply. The lower and upper ends of this band are encountered after a high-carbohydrate meal and an elevation in circulating fatty acids, respectively. Rates of oxidative utilization of the carbohydrate fuels glucose and lactate are reduced by increased fatty acid availability and oxidation by inhibition of pyruvate dehydrogenase (PDH) through the Randle cycle. Conversely, increases in availability of carbohydrate fuels together with increases in insulin result in decreased β-oxidation. Acute increases in malonyl-CoA levels appear to be the key factor in this reverse Randle cycle effect. The content of malonyl-CoA in perfused working hearts or in cardiac myocytes is increased with increasing glucose concentration (55), and this effect is mimicked by the PDH activator dichloroacetate (110). It has been suggested that this increase in malonyl-CoA is due to an increased supply of acetyl-CoA for ACC (110). However, there may be an additional effect at play. In my laboratory, we have observed that increasing glucose supply to isolated cardiac myocytes causes a decrease in the steady-state phosphorylation of Thr172 in the catalytic α-subunit of AMPK, resulting in both a decrease in AMPK activity and decreased phosphorylation of ACC (I. Tabidi & D. Saggerson, unpublished findings). The mechanism underlying this effect is not fully resolved at present, but it is independent of changes in the cellular AMP/ATP ratio and appears to be due to increased dephosphorylation of AMPK. In perfused hearts, insulin acutely increases ACC activity (45), and in both cardiac myocytes and perfused hearts, the hormone increases the malonyl-CoA content (6, 21, 55). These changes are attributable to a deactivation of AMPK (8, 21, 45) brought about by phosphorylation of the α-1/α-2 subunit isoforms of AMPK at Ser485/Ser491 by protein kinase B (*Akt*) (63). Increases in circulating fatty acids within the physiological range result in acute activation of cardiac AMPK, phosphorylation of ACC, and a decrease in malonyl-CoA (6, 21, 55). In essence, fatty acids can cause a feed-forward activation of their own oxidation mediated by the AMPK/ACC/malonyl-CoA/CPT1 axis. In addition, increased fatty acid supply attenuates the ability of insulin to inactivate AMPK (21, 37) and to raise malonyl-CoA (6, 21, 55). The regulatory network that sets the cardiac malonyl-CoA level is summarized in **Figure 3**. In cardiac ischemia, the balance of this network becomes disturbed. Because of the decrease in oxygen supply, AMPK activity is elevated, and this persists during reperfusion of the reversibly injured myocardium. This elevation of AMPK correlates with increased phosphorylation of ACC, resulting in decreased ACC activity, decreased malonyl-CoA content, and an increased rate of β-oxidation, which may contribute over 90% of the reperfused tissue's energy requirement (32, 78). As a consequence of the Randle cycle, there is inactivation of PDH, but at the same time AMPK enhances glucose transport and activates phosphofructokinase-2. This allows glycolysis, now uncoupled from glucose oxidation, to remain high, resulting in reduced pH recovery during reperfusion with ensuing contractile dysfunction (62). The elevated circulating level of NEFA under these circumstances exacerbates the problem. Recently developed pharmacological inhibitors of MCD, which increase malonyl-CoA level and lead to inhibition of β-oxidation and stimulation of glucose oxidation, offer the possibility of marked protection of the ischemic and postischemic heart (81).

The Role of Malonyl-CoA in Fuel Selection in Skeletal Muscle

In skeletal muscle, malonyl-CoA is involved both in reverse Randle cycle events and in fuel sensing during contraction. The content of malonyl-CoA is increased by glucose and insulin in an interdependent fashion, leading to decreased β-oxidation in rat soleus muscle

(118, 120), and is decreased in rat quadriceps muscle by fasting (87). These changes in malonyl-CoA are not accompanied by any alterations in the kinetic properties of ACC (120, 134) and have been suggested to reflect increased provision of acetyl-CoA and citrate, respectively the substrate and the allosteric activator of ACC. By contrast, in rat extensor digitorum longus muscle, an increase in malonyl-CoA in response to increased glucose was driven by a decrease in AMPK activity and decreased phosphorylation of ACC (64). It is not unreasonable to expect that there may be differences between skeletal muscle types in the way in which ACC activity is raised in response to glucose in order to increase malonyl-CoA provision. Hyperglycemia with hyperinsulinemia also results in increased malonyl-CoA and decreased long-chain fatty acid oxidation in human muscle (102). As has also been observed in the heart, physiological levels of long-chain fatty acids cause activation of AMPK, resulting in phosphorylation of ACCβ in skeletal muscle cells (36, 133). Considerable evidence suggests that malonyl-CoA levels are decreased in rat muscle during natural aerobic exercise or during experimental stimulation of contraction, thereby allowing the fueling of contraction by β-oxidation. Acute inactivation of ACC following activation of AMPK is generally agreed to contribute to the decrease in malonyl-CoA (see reviews by 58, 107), as also may acute activation of MCD (119). The content of malonyl-CoA in human muscle is markedly lower than in the rat, and some studies did not note any change in content during exercise. By contrast, other studies have shown that exercise results in increased AMPK activity, decreased ACC activity, and a decrease in malonyl-CoA content in human muscle (27, 44, 106). Interestingly, Holloway and colleagues (61) have reported a significant decrease in sensitivity to malonyl-CoA of human muscle CPT1B during aerobic exercise. Sustained elevations of malonyl-CoA have been suggested to be associated with insulin resistance in skeletal muscle. Ruderman and colleagues (108) have put forward the hypothesis that inhibition of CPT1 by malonyl-CoA would give rise to increased cytosolic long-chain fatty acyl-CoA resulting in a channeling of fatty acids into signaling glycerides, such as diacylglycerol and phosphatidic acid, leading to the pattern of activation of protein kinase C isoforms that is found in insulin-resistant muscle. Certainly, the content of long-chain fatty acyl-CoA shows a significant positive correlation with the content of malonyl-CoA in rat soleus muscle (5), but it is difficult unambiguously to translate these into cytosolic concentrations.

Malonyl-CoA and Insulin Secretion

Malonyl-CoA has been proposed to be a signal in glucose-stimulated insulin secretion (GSIS). This hypothesis proposes the existence of a glucose-sensing pathway in islet B cells that operates in parallel to the K_{ATP} channel-dependent pathway. The central feature of this hypothesis is that glucose metabolism results in an increase in malonyl-CoA which, through inhibition of CPT1, leads to a rise in cytosolic long-chain fatty acyl-CoA, which in turn can act as a coupling factor for insulin secretion. There is appreciable expression of ACC in B cells, and glucose metabolism is hypothesized to supply ACC with its acetyl-CoA substrate via PDH and with its citrate allosteric activator through an anaplerotic pathway. Inactivation of AMPK in response to glucose (122) may act to enhance ACC activity. Observations in support of this hypothesis are that expression of an ACC antisense construct and overexpression of MCD decreased malonyl-CoA content, increased β-oxidation, and decreased GSIS. Overexpression of CPT1 similarly decreased GSIS (for extensive literature on this hypothesis, see introductions in 60, 105). However, it should be pointed out that not all experimental findings are in accord with the above hypothesis (for example, see 69, 91).

Malonyl-CoA and the Hypothalamic Control of Food Intake

An increase in hypothalamic malonyl-CoA is associated with restraint of food intake. It is

suggested that a malonyl-CoA-induced inhibition of hypothalamic CPT1 results in increased cytosolic long-chain fatty acyl-CoA that activates K_{ATP} channels, resulting in neural stimulation that modifies food intake. The brain-specific CPT1C isoform is implicated in this response (135). At the level of the hypothalamus, both glucose and fatty acids decrease food intake. Glucose can increase the supply of acetyl-CoA for ACC to manufacture malonyl-CoA. Increased fatty acid levels can increase hypothalamic long-chain fatty acyl-CoA. Inactivation of hypothalamic AMPK by leptin and possibly by insulin and activation by ghrelin may also play a part in setting the level of malonyl-CoA through phosphorylation control of ACC. A recent review by Folmes & Lopaschuk (38) provides further information on this topic.

CONCLUDING REMARKS

The malonyl-CoA story has come a long way since the pioneering studies of Wakil, McGarry, and their colleagues, but I sense that there is still a great deal to discover. For example, our knowledge of the regulation of MCD is very incomplete. One intriguing question that still begs an answer is whether the isoforms of CPT1 are the sole targets of malonyl-CoA. Perhaps a full structural description of the malonyl-CoA binding sites in CPT1 will open the way for an informed search for similar malonyl-CoA binding motifs throughout the genome.

SUMMARY POINTS

1. Malonyl-CoA can be formed within mitochondria, peroxisomes, and the cytosol.
2. As well as being a metabolic intermediate in fatty acid biosynthesis in lipogenic tissues, cytosolic malonyl-CoA is an allosteric inhibitor of the mitochondrial outer membrane enzyme CPT1. CPT1 isoforms are widely expressed and are key regulatory enzymes for the mitochondrial β-oxidation of long-chain fatty acids.
3. Cytosolic malonyl-CoA levels are the result of the opposing activities of ACC and MCD that also are widely expressed in tissues and are regulated by many physiological factors.
4. Changes in physiological state bring about alterations in the sensitivity to malonyl-CoA of hepatic CPT1A that are driven by changes in the fluidity of the lipid core of the MOM.
5. The CPT1B isoform that is particularly expressed in muscle tissues is exquisitely sensitive to malonyl-CoA.

FUTURE ISSUES

1. Although we have considerable understanding of the acute regulation of ACC activity by allosteric and protein phosphorylation mechanisms, the questions of how and to what extent different forms of MCD are acutely regulated still need to be answered.
2. Information regarding the distribution of malonyl-CoA between intracellular compartments is currently lacking. Such information could help to explain how β-oxidation can proceed in muscle where malonyl-CoA appears to be at a concentration sufficient to totally inhibit CPT1B.
3. How the lipid core of the hepatic MOM changes with physiological state awaits explanation.

DISCLOSURE STATEMENT

The author is not aware of any biases that might be perceived as affecting the objectivity of this review.

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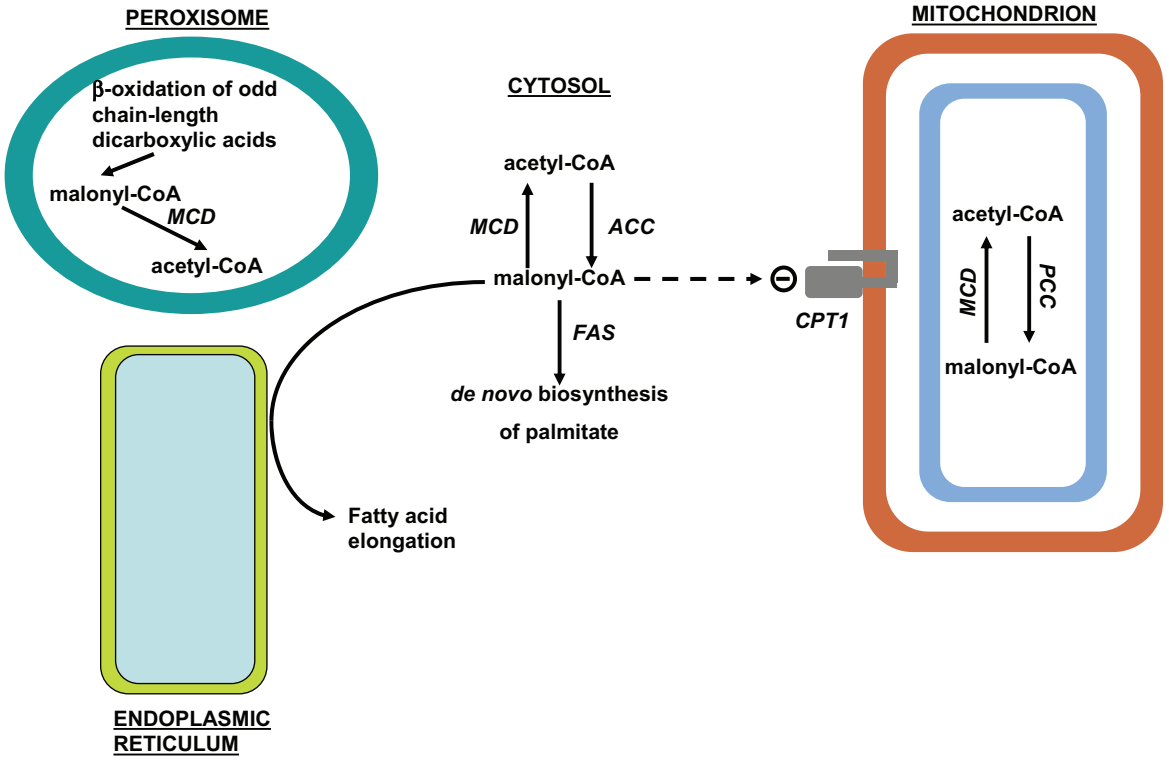

Figure 1

Summary of malonyl-CoA metabolism and its compartmentation in mammalian cells. Also shown is carnitine palmitoyltransferase 1 (CPT1), with an indication of its topology in the mitochondrial outer membrane and its inhibition by malonyl-CoA. ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; MCD, malonyl-CoA decarboxylase; PCC, propionyl-CoA carboxylase.

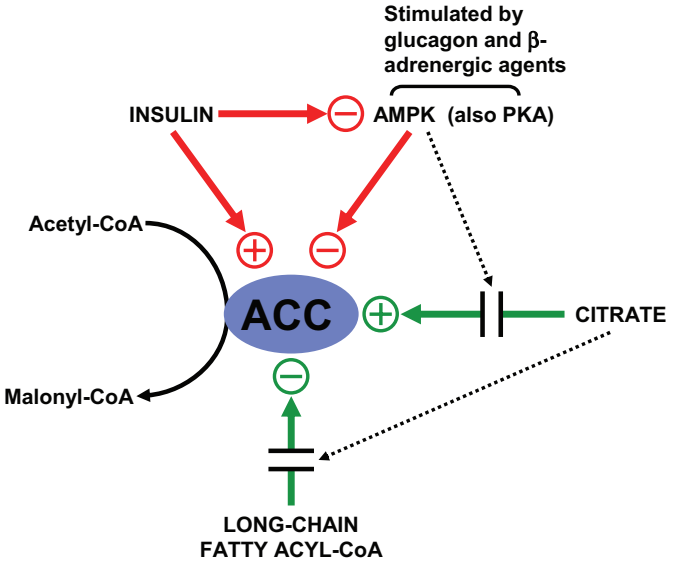

Figure 2

Regulation of hepatic acetyl-CoA carboxylase by allosteric effectors and protein phosphorylation. Allosteric effects and protein phosphorylation effects are shown in green and red, respectively. ACC, acetyl-CoA carboxylase; AMPK, adenosine monophosphate-activated protein kinase; PKA, protein kinase A.

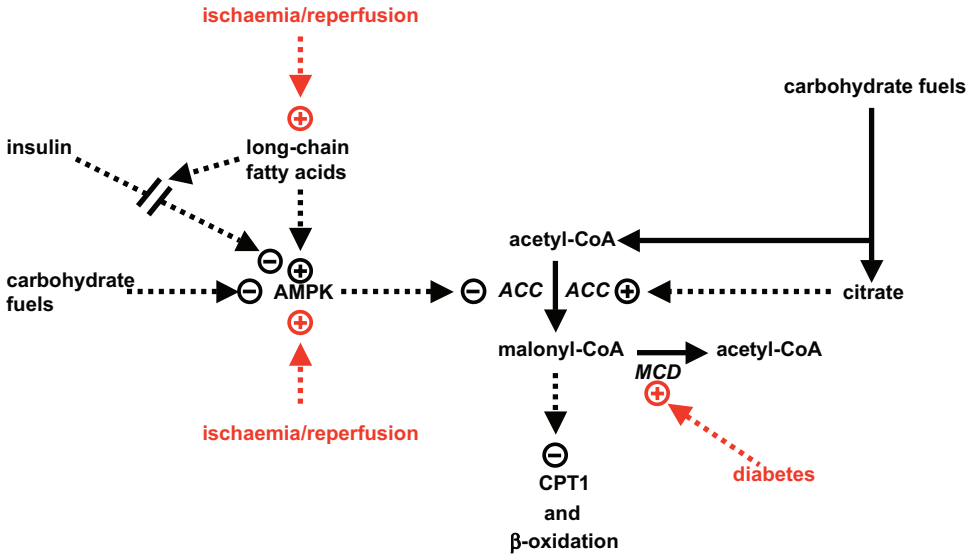

Figure 3

Physiological and pathological regulation of the malonyl-CoA level in cardiac muscle. Metabolic conversions are shown by bold arrows; regulatory effects are shown by dotted arrows. Pathological changes are in red. ACC, acetyl-CoA carboxylase; AMPK, adenosine monophosphate-activated protein kinase; CPT1, carnitine palmitoyltransferase; MCD, malonyl-CoA decarboxylase.

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Errata

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