

Myocardial Fatty Acid Metabolism in Health and Disease

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Lopaschuk GD, Ussher JR, Folmes CDL, Jaswal JS, Stanley WC. Myocardial Fatty Acid Metabolism in Health and Disease. *Physiol Rev* 90: 207–258, 2010; doi:10.1152/physrev.00015.2009.—There is a constant high demand for energy to sustain the continuous contractile activity of the heart, which is met primarily by the β -oxidation of long-chain fatty acids. The control of fatty acid β -oxidation is complex and is aimed at ensuring that the supply and

oxidation of the fatty acids is sufficient to meet the energy demands of the heart. The metabolism of fatty acids via β -oxidation is not regulated in isolation; rather, it occurs in response to alterations in contractile work, the presence of competing substrates (i.e., glucose, lactate, ketones, amino acids), changes in hormonal milieu, and limitations in oxygen supply. Alterations in fatty acid metabolism can contribute to cardiac pathology. For instance, the excessive uptake and β -oxidation of fatty acids in obesity and diabetes can compromise cardiac function. Furthermore, alterations in fatty acid β -oxidation both during and after ischemia and in the failing heart can also contribute to cardiac pathology. This paper reviews the regulation of myocardial fatty acid β -oxidation and how alterations in fatty acid β -oxidation can contribute to heart disease. The implications of inhibiting fatty acid β -oxidation as a potential novel therapeutic approach for the treatment of various forms of heart disease are also discussed.

I. INTRODUCTION

The heart has a very high energy demand and must continually generate ATP at a high rate to sustain contractile function, basal metabolic processes, and ionic homeostasis. In the normal adult heart, almost all (>95%) of ATP production is derived from mitochondrial oxidative phosphorylation (Fig. 1), with the remainder being derived from glycolysis and GTP formation in the tricarboxylic acid (TCA) cycle. The heart has a relatively low ATP content (5 $\mu\text{mol/g}$ wet wt) and high rate of ATP hydrolysis ($\sim 30 \mu\text{mol}\cdot\text{g wet wt}^{-1}\cdot\text{min}^{-1}$ at rest); thus under normal conditions, there is complete turnover of the myocardial ATP pool approximately every 10 s (428, 449–451). To sustain sufficient ATP generation, the heart acts as an “omnivore” and can use a variety of different carbon substrates as energy sources if available (358, 426, 538, 605). However, the adult heart normally obtains 50–70% of its ATP from fatty acid β -oxidation (46, 358, 428, 449, 450, 689).

The β -oxidation of fatty acids is under complex control and is dependent on a number of factors, including 1) fatty acid supply to the heart; 2) the presence of competing energy substrates (glucose, lactate, ketones, amino acids); 3) energy demand of the heart; 4) oxygen supply to the heart; 5) allosteric control of fatty acid uptake, esterification, and mitochondrial transport; and 6) the control of mitochondrial function, including direct control of fatty acid β -oxidation, TCA cycle activity, and electron transport chain (ETC) activity (136, 142, 312, 313, 358, 426, 538, 605, 609). The transcriptional control of enzymes involved in fatty acid metabolism and mitochondrial biogenesis are also important determinants of fatty acid β -oxidation rates. These regulatory steps will be briefly reviewed in this paper, and the reader is referred to a number of excellent reviews that address this regulation in more detail (126, 158, 159, 252, 379). These alterations in fatty acid β -oxidation can have significant energetic and functional consequences on the heart. In this review we concentrate on some of the recent advances made in understanding how these regulatory processes are altered in various pathological states, and how altering fatty acid β -oxidation can be used as an approach in the treatment of heart failure and ischemic heart disease.

II. REGULATION OF FATTY ACID β -OXIDATION IN THE HEART

A. Overview of the Fatty Acid β -Oxidation Pathway

The contribution of fatty acid β -oxidation to overall cardiac oxidative energy metabolism is very dynamic and can range from almost 100% of the total energy requirement of the heart to being a minor contributor (46, 428, 449, 450, 538). An overview of the fatty acid β -oxidative pathway is shown in Figure 2. Fatty acid use by the heart is dictated at many levels and is dependent on the source, concentration, and type of fatty acids delivered to the heart, as well as the presence of competing energy substrates. The regulation of fatty acid β -oxidation occurs at almost every step of the metabolic pathway, including at the level of lipoprotein lipase (LPL), fatty acid uptake into the cardiac myocyte, esterification to CoA, mitochondrial uptake, and β -oxidation. The rate of fatty acid β -oxidation is also very dependent on metabolic demand and the activities of the TCA cycle and ETC.

B. Source of Fatty Acids

Fatty acids are supplied to the heart as either free fatty acids (FFA) bound to albumin or as fatty acids released from triacylglycerol (TAG) contained in chylomicrons or very-low-density lipoproteins (VLDL) (143, 144, 660). Both sources significantly contribute to overall fatty acid supply to the cardiac myocyte. Normal circulating FFA concentrations range between 0.2 and 0.6 mM (609). However, these levels can dramatically vary from very low concentrations in the fetal circulation (191) to over 2 mM during severe stresses such as myocardial ischemia and uncontrolled diabetes (315, 316, 359). Activation of the sympathetic nervous system can also rapidly increase circulating FFA concentrations, primarily resulting from β -adrenoceptor-mediated stimulation of hormone-sensitive lipase activity in the adipose tissue (315). Increased sympathetic nervous system activity during and after a myocardial ischemic insult (315, 316, 419, 444), or with chronic heart failure (609), dramatically increases

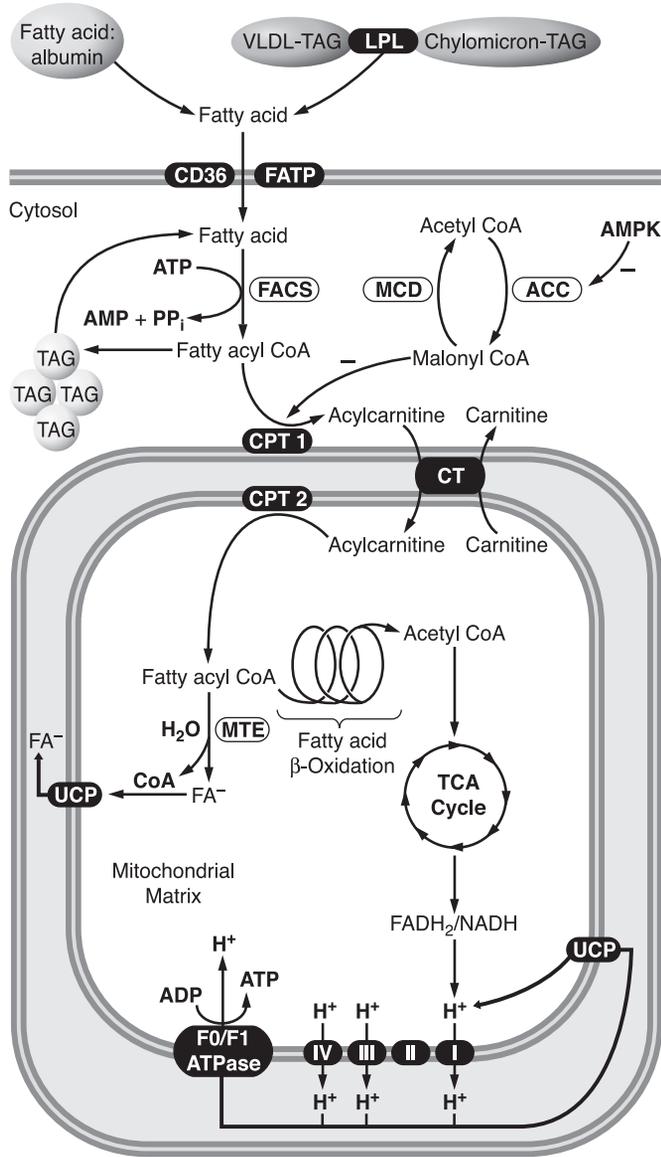


FIG. 1. Overview of fatty acid β -oxidation in the heart. Fatty acids utilized for cardiac fatty acid β -oxidation primarily originate from either plasma fatty acids bound to albumin or from fatty acids contained within chylomicron or very-low-density lipoproteins (VLDL) triacylglycerol (TAG). Fatty acids are taken up by the heart either via diffusion or via CD36/FATP transporters. Once inside the cytosolic compartment of the cardiac myocyte, fatty acids (bound to fatty acid binding proteins) are esterified to fatty acyl CoA by fatty acyl coA synthase (FACS). The fatty acyl CoA can then be esterified to complex lipids such as TAG, or the acyl group transferred to carnitine via carnitine palmitoyltransferase (CPT) 1. The acylcarnitine is then shuttled into the mitochondria, where it is converted back to fatty acyl CoA by CPT 2. The majority of this fatty acyl CoA then enters the fatty acid β -oxidation cycle, producing acetyl CoA, NADH, and FADH₂. Under certain conditions, mitochondrial thioesterase (MTE) can cleave long-chain acyl CoA to fatty acid anions (FA⁻), which may leave the mitochondrial matrix via uncoupling protein.

nant of the rate of myocardial fatty acid uptake and oxidation (44, 325, 688). Chronically elevated circulating FFA levels in obesity and diabetes are also an important determinant of the high rates of uptake and β -oxidation observed in these pathophysiological states (see sect. III).

Chylomicron TAG is also an efficient source of fatty acids that can compete with FFAs bound to albumin (28, 227, 437). Fatty acids contained in VLDL TAG can also be used for fatty acid β -oxidation. However, the majority of fatty acids used by the heart that originate from exogenous TAG are derived from chylomicrons, with only a minor portion originating from VLDL (227, 437). The activity of LPL is responsible for the majority of FFA derived from chylomicrons, and these chylomicron-derived FFAs are channeled primarily into fatty acid β -oxidation (437). In contrast, VLDL/apolipoprotein E (apo E) receptors have been demonstrated to be expressed in the heart (629, 630, 638), and the uptake of VLDL by this route has been proposed to be a possible source of myocardial fatty acids (278, 437). Indeed, a significant proportion of fatty acids derived from VLDL TAG may be mediated by VLDL/apo E receptor uptake of the VLDL, such that VLDL-derived fatty acids are equally distributed between β -oxidation and deposition into intramyocardial lipids (437). This has potentially important implications in the development of cardiac lipotoxicity (485).

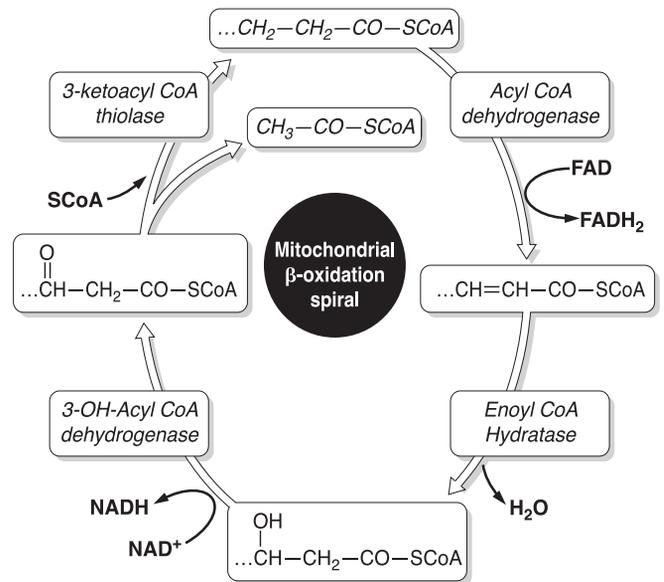


FIG. 2. Fatty acid β -oxidation in the heart. Fatty acid β -oxidation involves four enzymes (acyl CoA dehydrogenase, enoyl CoA hydratase, 3-OH acyl CoA dehydrogenase, and 3-keotacyl CoA thiolase), which exist in the heart as different isoforms with varying fatty acid chain length specificities. One cycle of the β -oxidation spiral results in the production of acetyl CoA (which then enters the TCA cycle) and a fatty acyl chain which is two carbons shorter.

circulating FFA concentrations. These chronic or acute increases in circulating FFAs have a major impact on the rates of cardiac fatty acid uptake and β -oxidation, as arterial fatty acid concentration is the primary determi-

C. Lipoprotein Lipase

Since the majority of circulating FFAs are present as TAG in lipoproteins, the hydrolysis of this TAG by LPL is an important determinant of overall fatty acid uptake and β -oxidation by the heart (332, 490). The primary endogenous tissue lipase, adipose triacylglycerol lipase (ATGL), also contributes to mitochondrial fatty acid uptake and oxidation in the heart (206) and will be discussed in further detail in section III D. With regard to LPL, functional LPL present on the capillary endothelial cell surface is initially synthesized as an inactive monomeric proenzyme in the endoplasmic reticulum (ER) of the cardiac myocyte itself (for review, see Ref. 490). Subsequently, the proenzyme is activated between the ER and the Golgi prior to being secreted as an active homodimer, following which it binds to cardiac myocyte cell surface heparin sulfate proteoglycans (HSPG) (490). LPL is subsequently transferred to luminal endothelial cell HSPG sites, by a mechanism that has yet to be identified. Degradation of LPL occurs either as a result of detachment from the HSPG binding sites and release into the bloodstream, or by internalization of the HSPG-LPL complex into the endothelial cell or cardiac myocyte compartment (490).

Alterations in the synthesis, activation, secretion, transport, capillary luminal binding, or degradation of LPL can significantly impact myocardial fatty acid supply, uptake, and β -oxidation. In general, conditions associated with increased LPL activity are associated with an increase in fatty acid β -oxidation. For instance, fasting results in an augmented LPL activity, which in part may be mediated by transport of cardiac LPL to the luminal surface of the endothelium, a process that may be stimulated by AMP-activated protein kinase (AMPK) (15). In contrast, in adipose tissue, LPL secretion decreases, which is associated with an angiotensin-like protein 4 promotion of active dimerized LPL conversion to the inactive monomer (619). Although the data are variable, diabetes and insulin resistance are also associated with an increase in the amount of cardiac LPL present on the luminal surface of endothelial cells, an effect accompanied by a decrease in cardiac myocyte LPL, thereby suggesting increased secretion of LPL (see Ref. 490 for review). Overexpression of cardiac LPL in mice is associated with adaptations in the myocardium similar to diabetes, including increased fatty acid uptake and the development of cardiomyopathies (700). In contrast, increases in circulating fatty acids, which compete with LPL-derived fatty acids for myocardial uptake, can displace LPL from its HSPG binding sites (554) and therefore effectively decrease LPL activity. Since FFA concentrations are often elevated in diabetes and insulin resistance, the contradictory data regarding the regulation of LPL in diabetes and insulin resistance may be partly explained by increased fatty acid induced release of luminal LPL.

D. Myocardial Fatty Acid Uptake

FFAs originating from either albumin or lipoprotein-TAG enter the cardiac myocyte either by passive diffusion or via a protein carrier-mediated pathway (see Refs. 192, 566, 615, 660). These protein carriers include fatty acid translocase (FAT)/CD36, the plasma membrane isoform of fatty acid binding protein (FABPm), and fatty acid transport protein (FATP) 1/6. A proposed mechanism for this protein-mediated uptake involves binding of the fatty acids to FABPm, which concentrates the fatty acids for either passive diffusion or uptake via FAT/CD36- or FATP 1/6-mediated uptake (566). Of these potential carriers, FAT/CD36 has received the most attention and plays a major role in the translocation of fatty acid across the sarcolemmal membrane of cardiac myocytes (209, 224, 376). Studies involving either FAT/CD36 inhibition (376) or deletion (311) have shown that 50–60% of fatty acid uptake and oxidation by the heart occurs via FAT/CD36-mediated transport. Patients with CD36 deficiency have low rates of myocardial fatty acid tracer uptake (176, 438, 677), consistent with a key role for CD36 in regulating cardiac fatty acid metabolism *in vivo*.

Unlike FATP or FABPm, FAT/CD36 can translocate between intracellular endosomes and the sarcolemmal membrane, which appears to be important in the regulatory control of fatty acid uptake (376). Both contraction and insulin stimulate FAT/CD36 translocation to the sarcolemmal membrane, thereby facilitating fatty acid uptake. The mechanism by which this occurs has still not been delineated, although contraction-induced translocation has been proposed to occur via activation of AMPK (376). Polyubiquitination of FAT/CD36 has recently been shown to regulate protein levels in the cell by targeting the protein for degradation (595). Insulin attenuates ubiquitination, which would theoretically attenuate proteosomal degradation, thereby increasing the availability of CD36 for translocation to the sarcolemmal membrane. In contrast, fatty acids enhance ubiquitination, thereby increasing FAT/CD36 degradation. This latter effect may be a mechanism for feedback inhibition of fatty acid uptake during the accumulation of intracellular fatty acid.

Although initial proposals suggested that the bulk of cardiac myocyte fatty acid transport may be due to passive diffusion and a flip-flop phenomena due to the lipophilic nature of fatty acids, we believe it is important to stress here that early studies done in cultured cardiac myocytes (169, 374, 566, 599, 613), and the majority of isolated heart studies (253, 311, 566), support the concept of a protein receptor-mediated transport process.

E. Myocardial Triacylglycerol Metabolism

The myocardium has labile stores of TAG that serve as an endogenous source of FFAs. Myocardial cytosolic

long-chain acyl CoA can be converted to TAG by glycerolphosphate acyltransferase (105, 358, 660), and since $\sim 80\%$ of long-chain fatty acids rapidly appear as CO_2 in coronary venous blood, one can assume that $\sim 20\%$ enters the intramyocardial TAG pool (609, 688). In healthy people, the intramyocardial content of TAG is low ($\sim 3 \text{ mg/g}$ tissue) (218) relative to the rate of FFA uptake ($\sim 3 \text{ mg}\cdot\text{g}^{-1}\cdot\text{h}^{-1}$) (118, 429). If 20% of the cardiac FFA uptake enters the intramyocardial TAG pool (358, 688), the mean turnover time for intramyocardial TAG is 5 h, which reflects the dynamic nature of myocardial TAG metabolism. Studies in rat hearts illustrate the relative importance of endogenous TAG breakdown to myocardial energy metabolism: fatty acids derived from endogenous TAG represented 36% of the energy expenditure in hearts perfused with glucose as the sole substrate, decreasing to $\sim 11\%$ when palmitate is added to the perfusate (538). Intramyocardial TAG degradation is accelerated by adrenergic stimulation (309) and synthesis is increased with elevated plasma FFA concentrations (diabetes, fasting, or starvation) (123, 321, 452). Plasma FFA concentration is a major regulator of intramyocardial TAG content, as recently shown using NMR spectroscopy in healthy humans, where there was a 70% increase in intramyocardial TAG content with short-term restriction of energy intake, and 260% with starvation, which corresponded with an elevation in plasma FFA concentrations (218).

Part of the breakdown of intracellular TAG is catalyzed by hormone-sensitive lipase, which is activated by cAMP. β -Adrenergic stimulation in isolated cardiac myocytes activates glycerolphosphate acyltransferase and incorporates palmitate into TAG stores while simultaneously increasing TAG breakdown (625), suggesting that adrenergic stress increases turnover of the intramyocardial TAG pool. A similar acceleration of both lipolysis and TAG synthesis was observed in the isolated perfused working rat heart when cardiac power was increased by a β -adrenergic agonist (195, 197).

F. Cytoplasmic Control of Fatty Acid β -Oxidation

Once in the cytoplasm, fatty acids are converted into long-chain acyl CoA esters by fatty acyl CoA synthetase (FACS) (Fig. 1). These long-chain acyl CoAs can then be used for synthesis of a number of intracellular lipid intermediates, or the fatty acid moiety can be transferred to carnitine and taken up into the mitochondria. The conversion of fatty acids into complex lipids such as TAG, diacylglycerol (DAG), and ceramides has recently received considerable interest, as the accumulation of these intermediates has been implicated in the development of insulin resistance, cardiac dysfunction, and heart failure (see Fig. 3 and Refs. 420, 480, 588, 621 for reviews). Of importance is that fatty acid supply and the rate of long-

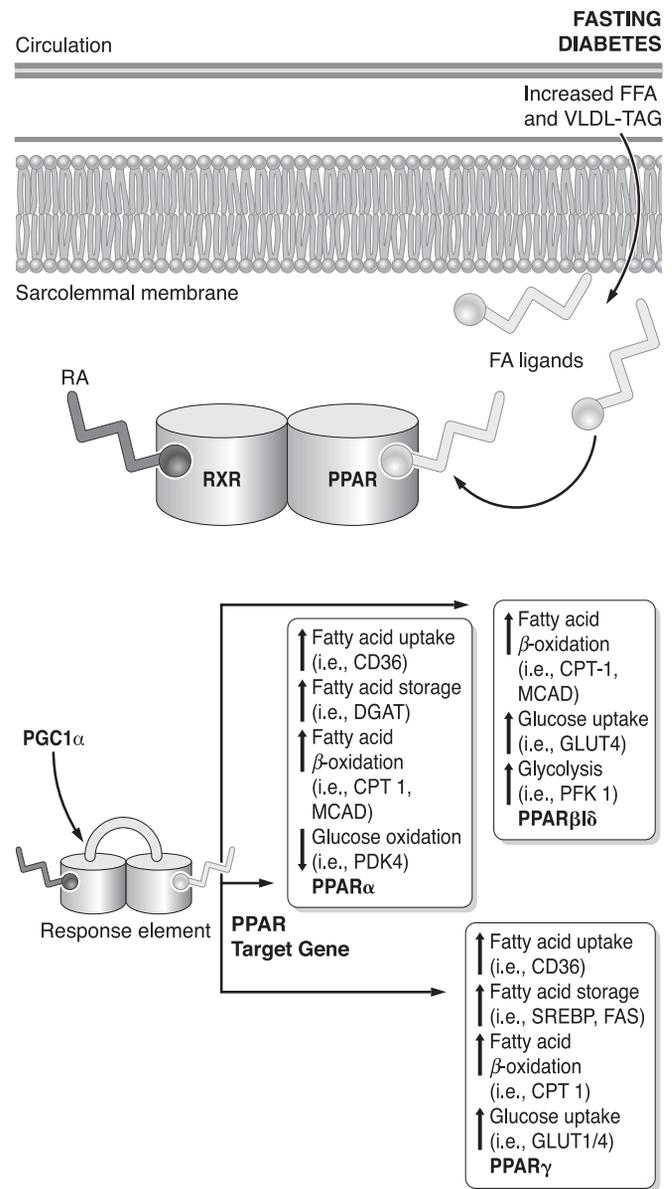


FIG. 3. Peroxisome proliferator activated receptor (PPAR) transcription factor family. In the physiological and pathophysiological setting of fasting/obesity/diabetes, increased circulating free fatty acids (FFAs) and very-low-density lipoprotein (VLDL)-derived triacylglycerol (TAG) concentrations increase lipid supply to the cardiac myocyte. This increases the availability of fatty acid ligands for binding to PPAR ($\alpha/\beta/\delta/\gamma$) receptors, which form heterodimeric complexes with the retinoid X receptor (RXR). The PPAR-RXR heterodimer complex then translocates into the nucleus where it binds to its appropriate response elements. In addition, numerous coactivator proteins, such as PPAR- γ coactivator 1 α (PGC1 α), play a central role in PPAR-mediated transcription, as they enhance the ability of the PPARs to increase transcription of their target genes. These target genes include a number of genes involved in regulating fatty acid storage [e.g., PPAR α -diacylglycerol acyl transferase (DGAT)], fatty acid oxidation [e.g., PPAR $\alpha/\beta/\delta/\gamma$ -medium-chain acyl CoA dehydrogenase (MCAD)], as well as glucose metabolism [e.g., PPAR α -pyruvate dehydrogenase kinase 4 (PDK4)].

chain acyl CoA production can impact the level of these potentially harmful intracellular intermediates. For example, mice with supraphysiological cardiac overexpression

of either FACS (335) or FATP1 (90) increases cardiac fatty acid uptake and conversion to long-chain acyl CoA, which results in the cytoplasmic accumulation of lipid, myofibrillar disorganization, and development of severe dilated cardiomyopathy. It is also possible that a decrease in the rate of long-chain acyl CoA removal by fatty acid β -oxidation may also contribute to lipotoxicity; however, this has yet to be established, and there is growing evidence that this is not the case (139, 345, 441). In the normal heart, $\sim 75\%$ of the fatty acids taken up are immediately oxidized (358, 428, 688). As a result, a decrease in fatty acid β -oxidation could theoretically contribute to lipid-induced cardiac pathology, and the acceleration of fatty acid β -oxidation may lessen the potential for lipotoxicity. However, the role of fatty acid β -oxidation rates in contributing to lipid-induced cardiac pathology is controversial (26, 360, 573, 702, 710, 712) and will be discussed in section III D.

G. Mitochondrial Fatty Acid Uptake

Carnitine palmitoyltransferase (CPT) 1 is a key enzyme in the mitochondria and catalyzes the conversion of long-chain acyl CoA to long-chain acylcarnitine, which is subsequently shuttled into the mitochondria. Allosteric inhibition of CPT 1 by malonyl CoA is a key mechanism by which CPT 1 activity is regulated (391, 393–397, 473, 543) (Fig. 1). The turnover of malonyl CoA in the heart is quite rapid, with a $t_{1/2}$ of ~ 1.25 min (511). Therefore, myocardial malonyl CoA concentrations are dependent on the balance between its synthesis from acetyl CoA via acetyl CoA carboxylase (ACC) (30, 138, 362, 370, 537) and its degradation via malonyl CoA decarboxylase (MCD) (135, 140, 142, 315, 545, 660). Two cardiac isoforms of ACC exist, ACC α and ACC β , with ACC β predominating (6, 39, 106, 116, 117, 140, 447). We (178, 362, 370, 537) and others (11) have provided direct evidence that ACC activity is inversely related to fatty acid β -oxidation in the heart. A role of ACC in regulating skeletal muscle fatty acid β -oxidation has also now been demonstrated (317, 683, 685). ACC β -deficient mice (7) have marked increases in muscle fatty acid β -oxidation rates, confirming the role of ACC β as a key regulator of fatty acid β -oxidation in muscle.

A key determinant of ACC activity in the heart is the activity of AMPK (141, 222, 223). In rat heart we demonstrated that AMPK is able to phosphorylate both ACC α and ACC β , resulting in an almost complete loss of ACC activity (140, 312, 314). Moreover, heart ACC copurifies with the $\alpha 2$ isoform of the catalytic subunit of AMPK (140), suggesting a tight association between AMPK and ACC in the heart. A close correlation also exists between increased AMPK activity, decreased ACC activity, and increased fatty acid β -oxidation in the heart (312, 314, 381) and in skeletal muscle (530, 684).

We have demonstrated that the heart has a high activity and expression of MCD (135), which consists of a 50-kDa protein that forms a tetramer in the intact cell (136, 667). The human MCD cDNA has two putative 5' start sites that code for a 54- and 50-kDa protein and contains a mitochondrial targeting sequence on the NH₂ terminus (101, 136, 162, 261, 667). Both isoforms of MCD are expressed in the heart, with the 50-kDa isoform being localized to the mitochondria (550). Although originally reported to be solely a mitochondrial enzyme in mammalian cells (112, 302), MCD is also found in the cytoplasm and peroxisomes (11, 290, 550). Interestingly, it has recently been suggested that as much as 50% of the malonyl CoA in the heart is derived from peroxisomal acetyl CoA production (512). In support of this observation, our recent work suggests that cardiac MCD is localized to peroxisomes, suggesting that both peroxisomal MCD and malonyl CoA have, as of yet, unidentified roles in controlling the rate of myocardial mitochondrial fatty acid β -oxidation (unpublished data). A number of studies have now shown that conditions associated with increased fatty acid β -oxidation are also associated with increased MCD activity, including fasting, diabetes, ischemia, and newborn heart development (30, 135, 196, 314). In skeletal muscle, liver, and pancreatic islet cells, increased MCD activity is also associated with increased fatty acid β -oxidation rates (21, 468, 530, 544).

AMPK acts as a "fuel sensor" that increases fatty acid β -oxidation during times of increased energy demand, or decreases fatty acid β -oxidation in times of low demand, secondary to respective decreases and increases in ACC activity and malonyl CoA levels. In skeletal muscle, it has also been suggested that MCD is a direct target of AMPK (544), whereby AMPK-induced phosphorylation of MCD increases MCD activity and subsequently lowers malonyl CoA levels; however, our laboratory and others have been unable to reproduce these findings (205, 550). AMPK is a serine/threonine kinase that responds to metabolic stresses that deplete cellular ATP, increase AMP, or increase the creatine/phosphocreatine (Cr/PCr) ratio (141, 220, 221, 223) and is very active in the heart with an important role in regulating both fatty acid β -oxidation (178, 312, 313, 370, 380, 381, 545), as well as glucose uptake and glycolysis (35, 160, 262–264, 340, 534, 622, 690, 698, 701). AMPK is a heterotrimeric protein, consisting of an α catalytic subunit and β and γ regulatory subunits. A number of different isoforms of each of these subunits exist, with a variable tissue distribution (116, 141, 179, 215, 221, 695, 696). Heart expresses both $\alpha 1$ and $\alpha 2$ catalytic subunits, with the $\alpha 2$ subunit predominating, as well as both the $\beta 1$ and $\beta 2$ subunits, and $\gamma 1$ and $\gamma 2$ subunits. The β and γ subunits regulate the catalytic activity of the α subunit, with the γ subunit being important in conferring the AMP sensitivity of the AMPK complex (141). While AMPK activation usually requires changes in the ratio of AMP/ATP

or Cr/PCr, it is now clear that cardiac AMPK activity can also be altered without changes in nucleotide levels (14, 312). For instance, insulin inhibits myocardial AMPK under conditions where AMP/ATP and Cr/PCr ratios do not change (35, 163, 178, 380). In addition, our lab (14) and others (34) have shown that during ischemia, the activation of the upstream AMPK kinase (AMPKK) also contributes significantly to the activation of AMPK. However, to date, the AMPKK responsible for AMPK activation during ischemia remains to be identified, as the identified AMPKKs, LKB1, and Ca^{2+} /calmodulin-dependent protein kinase kinase β (CaMKK β), are either not activated by ischemia (14) or expressed at very low levels in the heart (141), respectively. The most recent work in our lab has preliminarily identified the myosin light chain kinase to potentially be an AMPKK responsible for the activation of AMPK during ischemia (unpublished data).

H. Mitochondrial Fatty Acid Translocation

Following the formation of long-chain acylcarnitine by CPT 1, the acylcarnitine is translocated across the inner mitochondrial membrane by a carnitine:acylcarnitine translocase (CT) that involves the exchange of carnitine for acylcarnitine (Fig. 1). CT is a small protein (32.5 kDa) that has a broad specificity in transporting carnitine esters across the mitochondrial membrane, including acylcarnitine export from the mitochondria (354, 564). In addition to transporting acylcarnitines into the mitochondrial matrix, CT also provides free carnitine for subsequent CPT 1 reactions. CT is a critical step in the translocation of fatty acid moieties into the mitochondria, as evidenced by the development of cardiomyopathies and irregular heart beats in individuals with CT deficiencies (354).

Once in the matrix, acylcarnitine is converted back to long-chain acyl CoA by CPT 2, a 70-kDa enzyme located on the matrix side of the inner mitochondrial membrane (564). The long-chain acyl CoA produced by CPT 2 then enters the fatty acid β -oxidation pathway. Unlike CPT 1, CPT 2 is less sensitive to inhibition by malonyl CoA (393, 679, 680).

CD36 also resides in mitochondrial membranes in the heart, and it has been suggested to be essential for mitochondrial long-chain fatty acyl uptake and oxidation based on data using the putative CD36 inhibitor sulfo-*N*-succinimidyl oleate, which decreases fatty acid β -oxidation in skeletal muscle mitochondria (65). On the other hand, isolated cardiac and skeletal muscle mitochondria from CD36 knock-out mice have normal fatty acid β -oxidation and show a decrease in fatty acid β -oxidation with sulfo-*N*-succinimidyl oleate treatment that is similar to wild-type mice (295), suggesting that CD36 does not serve an essential role in mitochondrial fatty acid metabolism.

I. Fatty Acid β -Oxidation

The metabolism of long-chain acyl CoA in the mitochondrial matrix occurs via the β -oxidation pathway, involving the sequential metabolism of acyl CoAs by acyl CoA dehydrogenase, enoyl CoA hydratase, L-3-hydroxyacyl CoA dehydrogenase, and 3-ketoacyl CoA thiolase (3-KAT)(Fig. 2) (564). Each cycle of fatty acid β -oxidation results in the shortening of the fatty acyl moiety by two carbons, as well as the production of acetyl CoA, flavin adenine dinucleotide (FADH₂), and nicotinamide adenine dinucleotide (NADH). The four enzymes of β -oxidation exist in different isoforms that have different chain-length specificities. Each of these enzymes is sensitive to feedback inhibition by the products of the enzymatic reaction, including FADH₂ and NADH. Of particular importance is the feedback inhibition of 3-KAT by the accumulation of acetyl CoA. This is important in times of low metabolic demand, where a decrease in ETC and TCA cycle activity results in the accumulation of acetyl CoA, FADH₂, and NADH that feeds back and inhibits the enzymes of fatty acid β -oxidation (428). An increase in acetyl CoA and NADH production by the pyruvate dehydrogenase (PDH) complex can also directly inhibit fatty acid β -oxidation. As a result, flux through fatty acid β -oxidation is highly dependent on both cardiac energy demand and the source of carbon substrate (see sect. III).

The enzymes of fatty acid β -oxidation are also under a high degree of transcriptional control, and conditions that upregulate fatty acid β -oxidation are often associated with increases in the expression of a number of β -oxidation enzymes (360). These transcriptional changes are mediated to a large degree by the peroxisomal proliferator activated receptor (PPAR) α and peroxisomal proliferator-activated receptor γ coactivator-1 (PGC-1) α (126, 157–159, 252, 379).

The majority of fatty acids undergoing β -oxidation are not saturated fatty acids, but rather mono- or polyunsaturated fatty acids. For instance, the most abundant fatty acid in the blood is oleate, a monounsaturated fatty acid (453). The β -oxidation of these fatty acids is facilitated by auxiliary enzymes, which include 2,4-dienoyl CoA reductase and enoyl CoA isomerase (564). These enzymes facilitate the formation of a *trans* double bond from a *cis* double bond, which is necessary for the β -oxidation of fatty acids by the main enzymes involved in fatty acid β -oxidation (Fig. 2). Little is known as to whether these enzymes are important in determining the fate of saturated versus unsaturated fatty acids (i.e., oxidation or esterification into complex lipids). At equivalent, noncompeting concentrations, in isolated working rat hearts, the oxidation of unsaturated fatty acids such as oleate (Table 1) or arachidonic acid (540) occurs at similar rates to that of the saturated fatty acid palmitate.

TABLE 1. *Glucose oxidation in the presence of either palmitate or oleate in the isolated working mouse heart*

Palmitate Oxidation, nmol/g dry wt	Oleate Oxidation, nmol/g dry wt	Glucose Oxidation, nmol/g dry wt	
		With palmitate	With oleate
214 ± 25	247 ± 31	1,665 ± 257	1,887 ± 201

Isolated mouse hearts were perfused aerobically in the working mode for 30 min with either 5.0 mM glucose, 0.8 mM palmitate bound to 3% BSA, 100 μ U/ml insulin, and 2.5 mM Ca^{2+} , or 5.0 mM glucose, 0.8 mM oleate bound to 3% BSA, 100 μ U/ml insulin, and 2.5 mM Ca^{2+} .

Similar fractional β -oxidation rates are observed for palmitate and oleate in the human heart (688).

J. Transcriptional Control of Fatty Acid β -Oxidation

The enzymes involved in the oxidation of fatty acids are also under a high degree of transcriptional control, and conditions that upregulate fatty acid β -oxidation are often associated with increases in the expression of a number of these enzymes (126, 158, 252, 360, 703). Similarly, conditions in which fatty acid β -oxidation is low, such as in the fetal heart or during cardiac hypertrophy, are associated with a decreased expression of these enzymes. The transcriptional control of the enzymes of fatty acid β -oxidation is regulated in large part by nuclear receptor transcription factors that include the PPARs and PGC-1 α/β (see Refs. 126, 158, 252, 379, 703 for excellent reviews on this subject). The PPARs are members of a ligand-activated nuclear receptor superfamily that form a heterodimer with the retinoid X receptor and bind to the PPAR response element (PPRE) found on the promoter region of target genes and increase their expression (Fig. 3). The ligands for the PPARs include fatty acid and/or lipid metabolites such as the eicosanoids and leukotrienes (252).

PPAR α is a major transcriptional regulator of fatty acid metabolism and is abundantly expressed in heart muscle. PPAR α has been well studied, and its target genes include those encoding proteins involved in fatty acid uptake (FAT/CD36, FATP1), cytosolic fatty acid binding and esterification (FABP, FACS, glycerol-3-phosphate acyltransferase, diacylglycerol acyltransferase), malonyl CoA metabolism (MCD), mitochondrial fatty acid uptake (CPT 1), fatty acid β -oxidation [very-long-chain acyl CoA dehydrogenase, long-chain acyl CoA dehydrogenase, medium-chain acyl CoA dehydrogenase (MCAD), 3-KAT], mitochondrial uncoupling [including mitochondrial thiesterases (MTE-1) and uncoupling proteins (UCP2, UCP3)], and glucose oxidation [PDH kinase (PK) 4] (see Fig. 3 and Refs. 252, 703 for reviews). The importance of PPAR α

as a transcriptional regulator of cardiac fatty acid β -oxidation can be seen from “loss-of-function” and “gain-of-function” studies. Overexpression of PPAR α in the heart results in a marked increase in cardiac fatty acid uptake, fatty acid β -oxidation, and lipid overload due to an increased expression of the enzymes involved in these processes (160). The increase in fatty acid uptake and oxidation is exacerbated with the use of PPAR α ligands in these mice (160). In contrast, deletion of PPAR α (PPAR α $-/-$) results in decreased expression of fatty acid β -oxidation genes (676), which is accompanied by a decrease in fatty acid β -oxidation and a parallel increase in glucose oxidation (64). Such effects are associated with a significant improvement in the recovery of cardiac function during reperfusion following ischemia (548).

PPAR β/δ is a ubiquitously expressed nuclear receptor, which is present in high levels in the heart. PPAR β/δ has recently emerged as an important regulator of fatty acid β -oxidation and is involved in the transcriptional control of many of the same enzymes as PPAR α (Fig. 3). However, recent “loss-of-function” and “gain-of-function” studies on PPAR β/δ demonstrated a very different effect on phenotype compared with the PPAR α model. In the cardiac specific PPAR β/δ -deficient mouse (PPAR β/δ $-/-$), Cheng et al. (84) demonstrated a decrease in fatty acid oxidative enzymes, but this was associated with the development of a severe cardiomyopathy and an increase in myocyte lipid accumulation. In contrast, cardiac overexpression of PPAR β/δ in mice resulted in an increased expression of genes involved fatty acid β -oxidation and no evidence of lipid accumulation or cardiac dysfunction (61). Surprisingly, these mice also showed an increased cardiac glucose uptake and oxidation, a phenotype opposite of PPAR α overexpression. The reasons for these phenotypic differences are not clear, except that unlike PPAR α overexpression, PPAR β/δ overexpression did not increase the expression of genes involved in fatty acid uptake or esterification.

PPAR γ is a third PPAR isoform that, until recently, was not thought to have direct effects on the heart, due to very low expression levels in the heart. PPAR γ is highly expressed in adipose tissue, and PPAR γ activation can dramatically decrease circulating fatty acid levels (379, 703). PPAR γ agonists, such as the thiazolidinediones, are widely used as insulin-sensitizing agents, which may in part be due to lowering circulating fatty acid levels. However, direct PPAR γ overexpression in the heart has recently been shown to produce a phenotype similar to PPAR β overexpression (i.e., increased expression of fatty acid β -oxidation genes, but an increased expression of glucose transporters) (598). Further studies are needed to clarify what role PPAR γ has in directly regulating cardiac fatty acid β -oxidation and the relationship between fatty acid β -oxidation and myocardial glucose use.

PGC-1 α and PGC-1 β are two transcriptional coactivators important in mitochondrial biogenesis and are highly expressed in cardiac tissue (488). The PGC-1 isoforms interact with transcription factors bound to specific DNA elements in the promoter regions of genes (158). PGC-1 coactivates many members of the nuclear receptor superfamily, including the PPARs, the estrogen-related receptors, and the nuclear respiratory factor-1. Upregulation of PGC-1 by physiological (exercise) or pathophysiological (fasting, diabetes) stimuli results in dramatic phenotypic changes such as increased mitochondrial biogenesis, fatty acid β -oxidation, and oxidative phosphorylation; while decreased PGC-1 expression (such as in the fetal heart, cardiac hypertrophy, and heart failure) has the opposite effect of decreasing fatty acid β -oxidation and mitochondrial biogenesis (see Ref. 158 for review). The role of altered PGC-1 in diabetes, obesity, and heart failure will be discussed in subsequent sections.

K. Fatty Acids and Cardiac Efficiency

Cardiac mechanical efficiency is defined as the ratio of external cardiac power to cardiac energy expenditure by the left ventricle (44, 45). As the heart meets the majority (>95%) of its energetic requirements under non-ischemic conditions via the oxidative metabolism of fatty acids and carbohydrates, one can estimate myocardial energy expenditure from the myocardial oxygen consumption ($\dot{M}\dot{V}O_2$). The external power of the left ventricle is higher for a given $\dot{M}\dot{V}O_2$ when the myocardium has low rates of fatty acid β -oxidation relative to glucose and lactate oxidation (62, 254, 298, 306, 322, 407, 409, 592, 609). The initial evidence for this phenomenon comes from studies that found that increasing the rate of fatty acid uptake of the heart by elevating plasma FFA concentrations with an infusion of heparin and TAG emulsion resulted in ~25% increase in $\dot{M}\dot{V}O_2$ without changing the mechanical power of the left ventricle (407, 409). Mechanical efficiency was also decreased with an acute elevation in plasma FFA concentrations in healthy humans (592) and pigs (306), and during moderate ischemia in dogs (298, 410). Furthermore, the inverse phenomenon is also observed: inhibition of fatty acid β -oxidation by 4-bromocrotonic acid decreased $\dot{M}\dot{V}O_2$ and improved mechanical efficiency of the left ventricle in the perfused rat heart (254). Similar findings were observed with an infusion of insulin and glucose in pigs under resting conditions (306), and with inhibition of CPT 1 under conditions of acute adrenergic stimulation with pressure overload (723). Increasing fatty acid β -oxidation at the expense of glucose oxidation does not alter the slope of the relationship between left ventricular (LV) work and $\dot{M}\dot{V}O_2$, but rather increases the estimated $\dot{M}\dot{V}O_2$ at zero work (306), suggesting that increased reliance on fatty acid β -oxidation increases ATP hydrolysis for noncontractile purposes. The

underlying mechanisms responsible for this phenomenon are generally attributed to a lower phosphate/oxygen (P/O) ratio for fatty acid metabolism, increased uncoupling of mitochondrial oxidative phosphorylation, and greater futile cycling.

1. P/O ratios

The P/O ratio of oxidative phosphorylation reflects the number of molecules of ATP produced per atom of oxygen reduced by the mitochondrial ETC (236) and varies according to the energy substrate used for the generation of mitochondrial reducing equivalents (NADH and FADH₂). Comparing fatty acid (e.g., palmitate) and glucose, the complete oxidation of 1 palmitate molecule generates 105 molecules of ATP and consumes 46 atoms of oxygen, whereas the complete oxidation of 1 molecule of glucose generates 31 molecules of ATP and consumes 12 atoms of oxygen. Therefore, although the use of fatty acids as a substrate clearly generates the greater amount of ATP, it comes at the expense of a greater oxygen requirement than the use of glucose. The fact that fatty acids are in a relatively reduced state compared with glucose accounts for the greater oxygen requirement. As such, the relative P/O ratio of palmitate is less than that of glucose, rendering it a less "oxygen-efficient" energy substrate for ATP synthesis. Furthermore, fatty acid β -oxidation is less efficient with regards to ATP synthesis as, prior to the generation of acetyl CoA for the TCA cycle, it generates FADH₂ as a reducing equivalent, in addition to generating NADH, whereas glucose metabolism (glycolysis and glucose oxidation, i.e., pyruvate oxidation) only generates NADH. The oxidation of NADH at complex I of the mitochondrial ETC is indirectly coupled to the production of ATP, while the oxidation of FADH₂ bypasses complex I and thus pumps fewer protons across the inner mitochondrial membrane, which contributes to fatty acids being less efficient for the generation of ATP than glucose. Therefore, at any given level of LV work, an increased reliance on fatty acids relative to glucose as a metabolic fuel (for example, in the setting of obesity, insulin resistance, diabetes, or reperfusion following ischemia) decreases cardiac efficiency. Interestingly, cardiac efficiency calculated on the basis of solely P/O ratios with the use of exclusively glucose or fatty acids (e.g., palmitate) as an energy substrate only differs by a theoretical value ranging from 10 to 12%. However, as noted above, the reported differences in cardiac efficiency are up to 25%; thus additional mechanisms must contribute to fatty acid-induced suppression of cardiac efficiency.

2. Mitochondrial uncoupling

Mitochondrial ATP synthesis via oxidative phosphorylation is critically dependent on the maintenance of an electrochemical proton gradient across the inner mito-

chondrial membrane, generated by the extrusion of protons from the matrix to the intermembrane space by complexes I, III, and IV (236, 273). The reentry of protons into the mitochondrial matrix via the F_0/F_1 -ATPase drives the generation of ATP (Fig. 4) (273).

Uncoupling proteins (UCP1–UCP5) are a family of mitochondrial transport proteins that provide an alternate means for the reentry of protons from the inter-membrane space to the mitochondrial matrix that is not coupled to the synthesis of ATP. These inner mitochondrial membrane-bound proteins have been shown to uncouple ATP synthesis from oxidative metabolism, subsequently dissipating energy as heat (Fig. 4) (529). Three related homologs have been cloned (UCP1, -2, and -3). UCP1 is highly expressed in brown adipose tissue, where it is involved in nonshivering thermogenesis but is not expressed in heart. UCP2 is a ubiquitously expressed isoform that minimizes generation of mitochondrial-derived reactive oxygen species (ROS) (74, 75, 133, 430, 466, 529, 636). UCP3, on the other hand, exhibits a more limited tissue distribution, being highly expressed in tissues with a high capacity for fatty acid β -oxidation, such as brown adipose tissue, skeletal muscle, and the heart (230, 529, 562). Initially it was thought that UCP3 acts as proton transporter; however, more recent data suggest that it is a fatty acid anion transporter (183–185, 268–270). UCP3 can translocate the fatty acid anion out of the mitochondrial matrix; once in the intermembrane space, the fatty acid anion can associate with a proton (183–186, 259, 268–270). The resulting neutral fatty acid species is able to “flip-flop” back into the mitochondrial matrix, where it relinquishes the proton. The net effect is a leak of protons, as with classic uncoupling, but with no net flux of fatty acids. While this clearly occurs, it may not play a major role, as many studies show no effect of UCP3 content on the P/O ratio in isolated mitochondria (99, 102, 291, 563, 663).

With increased fatty acid β -oxidation, the delivery of reducing equivalents (NADH and $FADH_2$) to the ETC and the generation of ROS such as the superoxide anion ($O_2^{\bullet-}$) is increased (53) from either complex 1 or 3 of the ETC (8, 53, 181, 349). Indeed, increased cardiac fatty acid utilization in hearts from leptin-deficient (*ob/ob*) and leptin receptor-deficient (*db/db*) mice is associated with increased $\dot{M}\dot{V}O_2$, ROS generation, and uncoupled respiration, as well as decreased rates of ATP synthesis and lower cardiac efficiency (243, 244). However, the expression levels of UCP3 are not increased. Unfortunately, it should also be noted that there is not a large amount of available data to support the concept of fatty acid oxidation increasing ROS generation and uncoupled respiration. Interestingly, $O_2^{\bullet-}$ can activate uncoupling proteins directly (145, 146) and indirectly via formation of lipid peroxidation products (421). This activation may feedback and uncouple oxidative phosphorylation, and thus

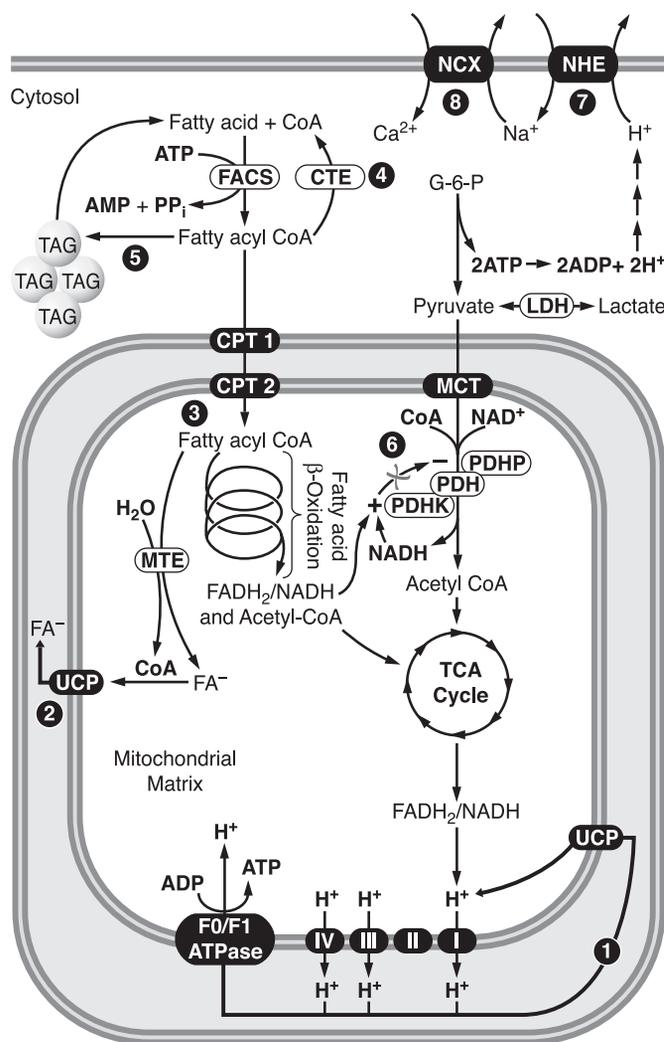


FIG. 4. Increased reliance of the myocardium on fatty acids decreases cardiac efficiency. The increased delivery of acetyl CoA to the tricarboxylic acid (TCA) cycle, and the subsequent delivery of reducing equivalents ($FADH_2$ and NADH) to the electron transport chain arising from increased fatty acid β -oxidation can reduce cardiac efficiency via the activation of uncoupling proteins (UCPs) that dissipate the mitochondrial proton (H^+) gradient and thus uncouple it from ATP synthesis (1). UCPs also contribute to the export of fatty acid (FA) anions generated in the mitochondrial matrix (2) due to the hydrolysis of matrix fatty acyl CoA(s) by mitochondrial thioesterases (MTEs) (3). FA anions are also generated in the cytosol due to the hydrolysis of cytosolic fatty acyl CoA(s) by cytosolic thioesterases (CTEs) (4). As mitochondria cannot regenerate fatty acyl CoA(s), FA anions require reesterification to CoA in an ATP-dependent manner via fatty acyl CoA synthase (FACS) prior to regaining entry into the mitochondria for β -oxidation. This futile cycling consumes ATP for noncontractile purposes. The cycling of fatty acids into and out of intramyocardial triacylglycerol (TAG) represents an additional route of futile cycling, where fatty acyl CoA molecules are the substrate for TAG synthesis, while the hydrolysis of TAG liberates fatty acids (5) that must be reesterified to CoA in an ATP-dependent manner by FACS prior to subsequent metabolism. Increased fatty acid β -oxidation also decreases cardiac efficiency by decreasing the activity of the pyruvate dehydrogenase complex (6) and hence the contribution of glucose oxidation to oxidative metabolism. This uncouples the processes of glycolysis and glucose oxidation and can increase the generation of cytosolic H^+ from the hydrolysis of glycolytically derived ATP. These H^+ can accumulate during ischemia and result in intracellular Na^+ overload (7), and trigger reverse mode Na^+/Ca^{2+} exchange during reperfusion (8). The reestablishment of ionic homeostasis consumes ATP and therefore decreases the amount of ATP available to fuel contractile function, ultimately decreasing cardiac efficiency.

further dissipate the generation of $O_2^{\bullet-}$ and protect the cell from excessive ROS generation; however, such an effect would increase $\dot{M}\dot{V}O_2$ and thus decrease cardiac efficiency.

It has been postulated that an additional role for UCP3 is to export fatty acid anions from the mitochondrial matrix when fatty acyl CoA levels are increased. When the supply of fatty acyl CoA exceeds the rate of fatty acid β -oxidation (250), MTE 1 can hydrolyze excess fatty acyl CoA, yielding free CoA and a fatty acid anion. Although not overtly apparent, this reaction may function to replenish intramitochondrial CoA for other CoA-dependent reactions, including reactions of the TCA cycle (α -ketoglutarate dehydrogenase), pyruvate oxidation (PDH), and fatty acid β -oxidation (3-KAT). As mitochondria do not have the capacity to regenerate fatty acyl CoA, the fatty acid anion is exported to the cytosolic compartment. It has been proposed that this export is mediated by UCP3, thus ridding the matrix of a potentially deleterious molecular species. Activation of PPAR α either pharmacologically or by diabetes causes a 3- to 10-fold increase in the activity and protein expression of MTE 1 and the rate of fatty acid extrusion from cardiac mitochondria in rats; however, the increase in UCP3 protein expression is more modest (~50%) (187, 296). This suggests that there is either sufficient UCP3 in the membrane to support the large increase in fatty acid export or that other protein(s) are responsible for this process. It has been postulated that mitochondrial CD36 could mediate fatty acid anion export from mitochondria; however, evidence against this comes from the observation that there is normal fatty acid anion export in mitochondria isolated from CD36 knock-out mice (295). In any case, the formation of fatty acids in the matrix by MTE 1 appears to function to protect against the depletion of matrix CoA (234); however, this would be associated with significant ATP wasting (see below) and hence contribute to the decrease in cardiac efficiency when fatty acid utilization is enhanced by decreasing the efficiency of converting ATP hydrolysis to contractile work.

3. Futile cycling

Increased fatty acid utilization can also decrease cardiac efficiency via the futile cycling of fatty acid intermediates, such that more ATP is consumed for noncontractile versus contractile purposes (Fig. 4). Export of fatty acid anions from the mitochondrial matrix by UCP3 generates a futile cycle: the exported fatty acid anion is converted to an acyl CoA ester prior reentry to the mitochondrial matrix for further metabolism via fatty acid β -oxidation. This process requires FACS, which consumes the equivalent of two molecules of ATP as the reaction releases AMP and pyrophosphate. Cytosolic thioesterases also exist and, in addition to other proposed

roles, have the potential to engage in the futile cycling of fatty acids (250), as the expression of these enzymes is increased in states of increased fatty acid utilization including starvation and diabetes mellitus, both of which decrease cardiac efficiency.

The cycling of fatty acids between their acyl moieties and the intracellular TAG pool represents another significant route of futile cycling. Although this mechanism may function to limit potentially deleterious increases in the cytosolic concentration of FFAs, it does at the expense of consuming ATP for noncontractile purposes (539). This is attributed to the liberation of FFAs from the TAG pool, which require reesterification via an ATP-dependent manner to form their respective acyl CoA moieties for subsequent β -oxidation or reincorporation into the TAG pool. The cycling of fatty acids and TAG has been reported to contribute to ~30% of total cellular energy consumption in isolated noncontracting cardiac myocytes (425). In addition, high concentrations of long-chain fatty acids can also activate sarcolemmal Ca^{2+} channels, which would increase the entry of extracellular Ca^{2+} into the cytosol and increase the rate of ATP hydrolysis required to maintain normal cytosolic Ca^{2+} homeostasis (248).

Elevated levels of fatty acids may impair contractile power by inhibiting the transfer of ATP from the mitochondrial matrix to the site of ATP hydrolysis in the cytosol, as suggested by studies demonstrating the inhibition of the adenine nucleotide translocator (ANT) by long-chain acyl CoAs (96, 323, 583, 585, 692). In vitro long-chain acyl CoAs inhibit ANT from either side of the mitochondrial membrane (96, 299, 323, 583–587, 693); however, inhibition from the matrix side is more pertinent to disease states like myocardial ischemia (323, 585, 587) and diabetes, where there is an increase in matrix long-chain acyl CoAs due to reduced β -oxidation and/or greater fatty acyl CoA supply to the matrix through the carnitine transport system.

L. Interaction Between Fatty Acid and Glucose Metabolism

In the well-perfused heart, ~50–70% of the acetyl CoA comes from β -oxidation of fatty acids and 30–50% comes from the oxidation of pyruvate (188, 605, 686, 687, 689) that is derived in approximately equal amounts from glycolysis and lactate oxidation (188, 605, 686, 687, 689). The pyruvate formed from glycolysis has three main fates: conversion to lactate, decarboxylation to acetyl CoA, or carboxylation to oxaloacetate or malate (Fig. 5). Pyruvate decarboxylation is the key irreversible step in carbohydrate oxidation and is catalyzed by PDH (470, 494), a multienzyme complex located in the mitochondrial matrix. PDH is under both phosphorylation and allosteric regulation. PDH is inactivated by phosphorylation on the

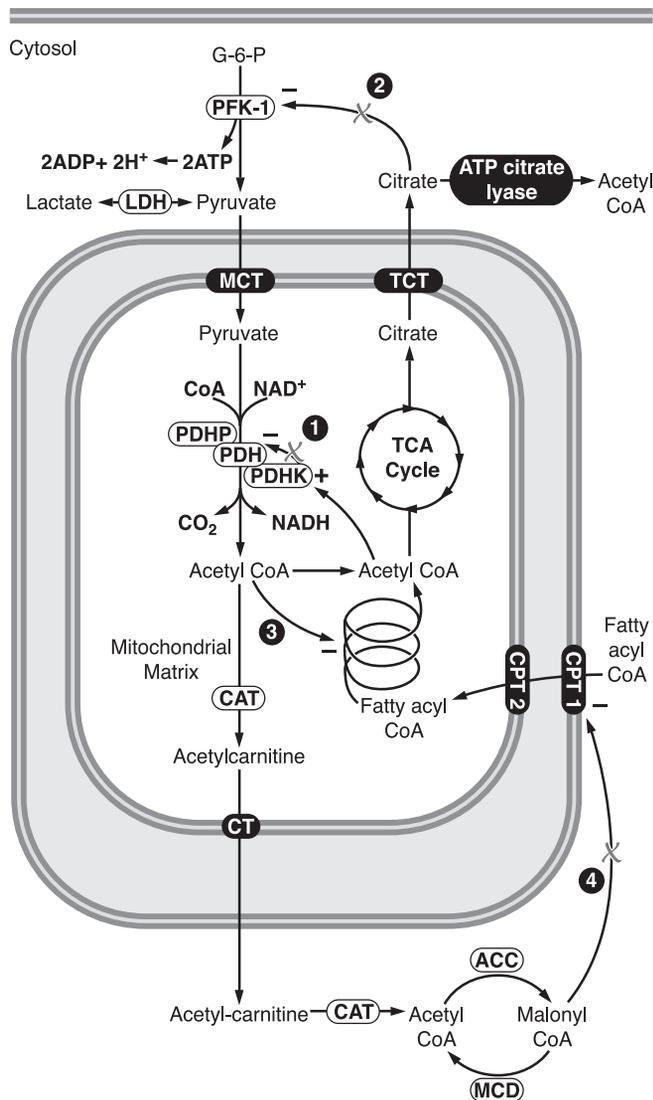


FIG. 5. The Randle (glucose-fatty acid) cycle. The Randle cycle describes the reciprocal relationship between fatty acid and glucose metabolism. The increased generation of acetyl CoA derived from fatty acid β -oxidation decreases glucose (pyruvate) oxidation via the activation of pyruvate dehydrogenase kinase (PDK) and the subsequent phosphorylation and inhibition of pyruvate dehydrogenase (PDH) (1). PDK is also activated by increased mitochondrial NADH/NAD⁺ ratios in response to increased fatty acid β -oxidation. The increased supply of fatty acid β -oxidation-derived acetyl CoA to the TCA cycle can also decrease glycolysis due to the inhibitory effects of citrate [a TCA cycle intermediate which has gained access to the cytosol via the tricarboylate carrier (TCC)] on phosphofructokinase-1 (PFK-1) (2). Citrate can also serve as a source of cytosolic acetyl CoA (see below). The inhibition of glucose (pyruvate) oxidation is the predominant inhibitory effect of fatty acid β -oxidation on the pathways of glucose metabolism. Conversely, the increased generation of acetyl CoA derived from glucose (pyruvate) oxidation inhibits fatty acid β -oxidation, as the terminal enzyme of fatty acid β -oxidation, 3-keto-acyl CoA thiolase, is sensitive to inhibition by acetyl CoA (3). Acetyl CoA derived from glucose (pyruvate) oxidation due to the activity of carnitine acetyl transferase (CAT) and subsequent formation of acetyl-carnitine is also a substrate for carnitine:acetyl-carnitine transferase (CACT). CACT exports acetyl-carnitine to the cytosol, where it can be reconverted to acetyl CoA through the activity of cytosolic CAT. Cytosolic acetyl CoA is a substrate for acetyl CoA carboxylase (ACC), which can increase the generation of malonyl CoA, an endogenous inhibitor of CPT I (4), and therefore decrease fatty acid β -oxidation when glucose (pyruvate) oxidation is increased.

E₁ subunit of the enzyme complex by a specific PDHK and is activated by dephosphorylation by a specific PDH phosphatase (289, 470, 681) (Fig. 3). PDK is inhibited by pyruvate and by decreases in the acetyl CoA/CoA and NADH/NAD⁺ ratios (289, 470, 681) (Fig. 3). There are four isoforms of PDK (PDK1–4); PDK4 is the predominant isoform in heart, and its expression is rapidly induced by starvation, diabetes, and PPAR α ligands (56, 225, 470, 697), suggesting that its expression is controlled by the activity of the PPAR α promoter system. High circulating FFAs and intracellular accumulation of long-chain fatty acid moieties, such as that occurring with fasting or diabetes, enhance PPAR α -mediated expression of PDK4, resulting in greater phosphorylation-induced inhibition of PDH and less oxidation of pyruvate derived from glycolysis and lactate (247, 697). The PDH complex also contains a PDH phosphatase that dephosphorylates and activates PDH. The activity of PDH phosphatase is increased by Ca²⁺ and Mg²⁺ (390).

The oxidation of pyruvate and the activity of PDH in the heart are decreased by elevated rates of fatty acid β -oxidation, such as those occurring when plasma concentrations of FFAs are elevated. In addition, pyruvate oxidation is enhanced by suppression of fatty acid β -oxidation, as observed with a decrease in plasma FFA concentrations, or by a direct inhibition of fatty acid β -oxidation (101, 232, 233, 310, 358, 565, 605). High rates of fatty acid β -oxidation also inhibit phosphofructokinase isoforms 1 and 2 (and thus glycolysis) via an increase in cytosolic citrate concentration. This “glucose-fatty acid cycle” was first described by Philip Randle and colleagues in the 1960s (182, 497, 498) and thus is generally referred to as the “Randle cycle.” The maximal rate of pyruvate oxidation at any given time is set by the degree of phosphorylation of PDH; however, the actual flux is determined by the concentrations of substrates and products in the mitochondrial matrix as these control the rate of flux through the active dephosphorylated complex (219).

M. Fatty Acid Metabolism During an Acute Increase in Work Load

During exercise, the healthy heart can increase LV contractile power and myocardial oxygen consumption four- to sixfold above resting values, which requires a proportional increase in the generation of NADH and FADH₂ from substrate oxidation. An acute increase in cardiac work load generally increases myocardial fatty acid uptake and β -oxidation. However, the relative increase is greater for carbohydrates (glucose, glycogen, and lactate) than for fatty acids with exercise in humans (188, 274, 275, 326, 327), or β -adrenergic stimulation and elevated afterload in large animals (572, 722, 723) or perfused rat hearts (106, 195, 197, 572, 722, 723). The

response in vivo is highly dependent on the arterial concentrations of lactate and FFA, as an increase in arterial lactate during exercise greatly increases myocardial lactate uptake at the expense of FFA (188). Similarly, with prolonged moderate intensity exercise (>30 min), there is increased FFA release from adipose tissue and elevated plasma FFA levels, which increases myocardial FFA uptake and β -oxidation (328). Treatment with nicotinic acid during exercise decreases arterial FFA concentrations, fatty acid uptake, and β -oxidation and increases glucose and lactate uptake (328), illustrating the clear role of arterial FFA levels in regulating substrate oxidation in the heart.

The increase in myocardial fatty acid uptake and β -oxidation during high work loads is accompanied by a decrease in myocardial malonyl CoA content after 15–30 min of stimulation in pigs (213, 294) and in perfused rat hearts (195, 196, 513), which suggests that removal of malonyl CoA inhibition of CPT 1 facilitates the increase in fatty acid β -oxidation. On the other hand, an abrupt increase in LV power in pigs induced by aortic contraction and β -adrenergic stimulation increases fatty acid β -oxidation 2.5-fold after 5 min despite a similar increase in myocardial malonyl CoA concentration. There is no increase in the activity of AMPK or MCD, and no change in ACC activity with an increase in cardiac energy expenditure (213, 294, 513, 723). Thus the increase in fatty acid β -oxidation with an acute increase in work load does not appear to be dependent on alternations in the ACC-MCD-malonyl CoA pathway.

N. Species and Insulin Sensitivity Differences in Control of Myocardial Fatty Acid Metabolism

Although we have discussed in great detail the control of myocardial fatty acid metabolism based on a vast number of comprehensive studies, there are a number of key differences between animal models utilized that need to be highlighted and that the reader must take into consideration when interpreting these data. First, isolated working rat hearts exposed to equivalent concentrations

of perfusate fatty acid will oxidize these fatty acids at significantly greater rates than their mouse counterparts (24, 137, 139, 312). This may appear somewhat unexpected, as the mouse has a substantially higher heart rate and work load, and thus must oxidize more energy to meet the energy needs required to sustain contractile function. However, glucose and lactate oxidation rates are dramatically higher in the mouse versus the rat, which accounts for the vast differences in work load and oxidative demand (166, 448). Furthermore, fatty acid-induced inhibition of glucose oxidation is much more potent in the rat (~10- to 15-fold, Ref. 538) than in the mouse (~3- to 5-fold, Ref. 164).

Interestingly, the mouse heart is also much more sensitive to insulin, as insulin results in a dramatic increase in glucose oxidation rates that is not inhibited to the same extent by high fatty acids in the perfusate, which is seen in the rat (164, 538). Moreover, insulin does not actually reduce myocardial fatty acid β -oxidation rates in the rat when the perfusate contains high levels of fat (538), whereas it causes a dramatic reduction in myocardial fatty acid β -oxidation rates in the mouse (164). This may be an important issue to consider with regard to the vast number of studies involving high-fat feeding, obesity, and diabetes in transgenic mouse models, which are likely not to be replicated in the rat (due to lack of transgenics in this species), yet may possibly yield completely different results due to species' differences in fatty acid regulation and insulin sensitivity of fatty acid metabolism.

III. METABOLIC PHENOTYPE IN OBESITY AND DIABETES: UNDERLYING MECHANISMS AND FUNCTIONAL CONSEQUENCES

Obesity and diabetes both induce a distinct cardiac metabolic phenotype (Table 2) that can result in an increase in fatty acid uptake and β -oxidation by the heart. The underlying mechanisms of this cardiac phenotype are complex but may include alterations in circulating concentrations of FFAs and adipokines, the expression and cellular localization of fatty acid transporters, use of en-

TABLE 2. Characteristics of the metabolic phenotype in obesity and diabetes

Measured Parameter	Obesity	Reference Nos.	Diabetes	Reference Nos.
Circulating FFAs and TGs	↑	13, 26, 60, 110, 276, 283, 371, 507, 637, 710	↑	26, 501, 710
Fatty acid uptake	↑	26, 51, 110, 305, 371, 482, 483, 501, 710	↑	29, 51, 67, 481, 482, 551
			ND	214, 260, 603
Intramyocardial TG	↑	26	↑	26, 123, 424, 440, 517, 541
Malonyl CoA concentration	↓	355	↓	214, 355, 545
MCD expression	↑	360	↑	545, 709
Fatty acid β -oxidation	↑	2, 3, 60, 387, 482	↑	2, 38, 67, 69, 207, 229, 244, 246, 292
Fatty acid β -oxidation	↓	710	↓	710

FFA, free fatty acid; TG, triglyceride; MCD, malonyl CoA decarboxylase; ↑, increase; ↓, decrease; ND, no difference.

ogenous stores of fatty acids for β -oxidation, and/or alterations in the regulation of fatty acid β -oxidation at both the enzymatic and transcriptional level. Of importance is that it is becoming clear that these changes in fatty acid metabolism can have a significant impact on cardiac function and efficiency in obesity and diabetes.

A. Alterations in Myocardial Fatty Acid Supply, Uptake, and β -Oxidation in Obesity and Diabetes

1. Fatty acid supply

Normally when the amount of energy entering the body exceeds the immediate energy expenditure, the excess energy is stored in adipocytes in the form of TAG. Under physiological conditions, the release of FFAs from adipose is well regulated such that appropriate amounts of FFAs are released to meet the energy requirements of tissues including the heart. When the balance between energy supply and demand is perturbed due to overconsumption of food, adipose tissue stores the excess lipid. When adipocyte size is greatly increased, there is "spillover" of lipids, such that circulating FFAs and TAG are elevated (47, 113, 203, 283, 307, 475, 501, 507). These elevated levels of FFAs can also accelerate VLDL TAG synthesis in the liver, further contributing to hyperlipidemia (339). Both human and animal studies have shown that a prevalent metabolic change in obesity involves an elevation in circulating FFAs and TAGs (60, 110, 276, 307, 371, 387, 620, 637, 710). In parallel with increasing circulating lipids, intramyocardial TAG content appears to increase progressively with body mass index (626). It has been proposed that accumulation of fatty acids and TAG in the myocardium may contribute to the development of cardiac dysfunction and heart failure (88, 89, 573, 648, 710, 712) (see sect. III D).

This increase in fatty acid supply to the heart can increase fatty acid uptake and β -oxidation in obesity and diabetes; however, additional mechanisms are also present. For instance, cardiac fatty acid β -oxidation is elevated in 4-wk-old *ob/ob* and *db/db* mice prior to a significant change in circulating substrates (60). A potential mechanism to explain the increase is an increase in LPL activity. However, the evidence for an increase in LPL activity in the diabetic heart is inconclusive (48, 301, 383, 431, 489, 521), potentially due to differences in the degree and duration of diabetes and method of LPL quantification (490). Nonetheless, it does appear that hearts from insulin-resistant animals have an enlargement of the coronary LPL pool (493), and acute and chronic moderate diabetes induced with streptozotocin is associated with an increased heparin-releasable LPL activity (489, 521), which could potentially contribute to the elevated rates of fatty acid β -oxidation.

2. Fatty acid uptake

Increased fatty acid uptake observed in obesity and diabetes may also be dependent on greater expression and localization of sarcolemmal fatty acid transporters. Cardiac fatty acid uptake is elevated in the insulin-resistant, obese Zucker rat, an effect associated with a greater amount of FAT/CD36 localized in the sarcolemma with no change in total cellular content (110, 371). Increased translocation of FAT/CD36 to the sarcolemma has also been observed in hearts from *db/db* mice (66). In addition, total protein and sarcolemmal content of FABPpm is also elevated. It has been previously demonstrated that an increase in FAT/CD36 and FABPpm content in the sarcolemmal membrane markedly increases fatty acid uptake in cardiac myocytes and giant sarcolemmal vesicle preparations (76) and that knockout of FAT/CD36 markedly impairs fatty acid β -oxidation in the working mouse heart (311). As a result, an increased expression and subcellular distribution of fatty acid transporters could partially account for the increased fatty acid supply and oxidation. The mechanism resulting in the relocation of fatty acid transporters to the sarcolemma is unknown. It has been proposed that hyperinsulinemia associated with obesity-induced insulin resistance and diabetes could contribute, as insulin stimulates the translocation of CD36/FAT to the sarcolemma in rat cardiac myocytes (304, 373, 376).

Previous reports suggest that decreased levels of FAT/CD36 may contribute to insulin resistance in the spontaneously hypertensive rat (10, 487). However, recent evidence suggests the opposite, that increased expression of FAT/CD36 contributes to insulin resistance, as there is a positive correlation between the sarcolemmal content of FAT/CD36 and cellular TAG in skeletal muscle from obese and type 2 diabetic patients (50, 551). Moreover, abnormal expression of FAT/CD36 in the liver during diet-induced obesity (DIO) causes dyslipidemia, contributing to the cardiac metabolic phenotype in obesity (305).

3. Endogenous TAG stores

The intramyocardial TAG content is highly labile and increases rapidly with short-term starvation or food restriction in humans (218) and rodents (452), presumably due to an increase in FFA and ketone bodies. Obesity and diabetes increase intramyocardial TAG stores (123, 424, 472, 516) due in part to elevated circulating FFAs and TAG (26, 424, 472, 516), increases in fatty acid uptake (109), and increased intramyocardial TAG synthesis due to increased myocardial CoA and long-chain acyl CoA synthesis (363, 367, 506). Despite the accumulation of TAG in the diabetic heart, these stores can be rapidly mobilized in the presence or absence of high concentrations of fatty acids (541). Hearts from diabetic rats also

display a greater rate of [^{13}C]palmitate enrichment and a greater rate of turnover of their endogenous TAG pool, which is associated with a greater oxidation of endogenous unlabeled fatty acids (439). Interestingly, even if diabetic rat hearts are perfused in the absence of exogenous fatty acids, glucose oxidation still provides <20% of the total ATP requirement of the heart (541, 669), suggesting that in addition to high circulating concentrations of FFAs, other mechanisms also contribute to the decrease in glucose metabolism. These additional mechanisms may include the interaction of fatty acid and glucose metabolism as defined by the Randle cycle, the potential implications of lipotoxicity on insulin signaling, as well as changes in the subcellular control of fatty acid β -oxidation.

4. Mitochondrial fatty acid uptake

Modifications in the malonyl CoA regulation of CPT 1 and the transport of fatty acids into the mitochondria play an important role in the accelerated rates of fatty acid β -oxidation found in obesity and diabetes. We have previously demonstrated that hearts from streptozotocin-treated rats are almost entirely dependent on fatty acid β -oxidation as a source of TCA cycle acetyl CoA when perfused with glucose and palmitate as working hearts with either diabetic or normal substrate concentrations (545). This reliance on fatty acid β -oxidation is not associated with changes in AMPK or ACC activity; however, MCD expression and activity are increased in the diabetic group (545). MCD mRNA levels are elevated in hearts from streptozotocin-treated rats (709), and malonyl CoA levels are decreased in hearts from streptozotocin-treated swine (214, 355). As MCD is the enzyme responsible for the degradation of malonyl CoA in the heart, this would suggest that a reduction in malonyl CoA levels and relief of inhibition of CPT 1 contribute to accelerated rates of fatty acid β -oxidation in diabetes.

Preliminary evidence also suggests that MCD plays a role in augmenting fatty acid β -oxidation in obesity, since mice subjected to DIO have elevated rates of fatty acid β -oxidation at the expense of glucose oxidation, and this is associated with an increased expression of MCD (165, 360). In addition, both high-fat feeding and fasting, which induce elevated FFA concentrations, result in increased MCD expression, potentially due to the activation of PPAR α (331, 709). MCD is highly regulated by PPAR α transcriptional control (114, 293, 331). We showed that cardiac MCD activity and expression are increased in diabetes, fasting, high-fat feeding, and newborn hearts (63, 136, 196, 314, 708). Supporting this concept, PPAR α null mice have increased rates of glucose oxidation and decreased expression and activity of MCD (64).

In contrast, the elevation in myocardial fatty acid β -oxidation observed in *db/db* mice is associated with a

reduction in AMPK activity and an increase in malonyl CoA content (66). Furthermore, although fatty acid β -oxidation contributes the majority of oxidative ATP production in the obese JCR rat (365), AMPK and ACC activity did not differ from their lean counterparts (26).

5. Fatty acid β -oxidation

Controversy exists as to whether the observed accumulation of intramyocardial lipid metabolites (TAG, long-chain acyl CoA, DAG, and ceramide) in obesity and type 2 diabetes is primarily due to an excessive fatty acid supply or to an impaired ability of the myocardium to oxidize the available fatty acids (151, 360, 573, 710, 712) (Fig. 6). Recently, a number of experimental studies suggested that decreased rates of fatty acid β -oxidation play a major role in the accumulation of intramyocardial lipid metabolites (243, 244, 573, 710, 712). A study in obese Zucker rats suggests that myocardial fatty acid β -oxidation is impaired following an overnight fast, which is associated with an increased lipid deposition in the heart and impaired contractile function (710). However, this study did not consider the contribution of the dramatically expanded intracellular pool of TAG as a source of fatty acid to overall fatty acid β -oxidation. In contrast, results from our laboratory with JCR obese rats demonstrate that fatty acid β -oxidation rates are not impaired following an overnight fast and that the doubling of intramyocardial TAGs observed in this model is likely due to an excessive fatty acid supply (26). Moreover, fatty acid β -oxidation accounts for the majority of ATP production in hearts from JCR obese rats (365). Cardiac overexpression of PPAR α , which produced a phenotype mimicking that seen in type 2 diabetes, is associated with a dramatic increase in fatty acid β -oxidation rates and a subsequent reduction in both glucose uptake and oxidation (160). Recent studies in our laboratory have demonstrated that mice subjected to DIO result in fatty acid β -oxidation being the major supplier of energy for the heart (Zhang L, Ussher J, Lopaschuk G. unpublished data). Supporting our findings, studies from Aasum and colleagues have also shown that fatty acid β -oxidation rates are enhanced in hearts from *db/db* mice and mice subjected to DIO (2, 3, 207, 245, 246, 324). Work from Abel and colleagues, as well as our laboratory, have also reproduced these findings in perfused hearts from *db/db* mice and *ob/ob* mice (60, 69, 387). In rodent models of type 1 diabetes, myocardial fatty acid β -oxidation rates are also significantly enhanced, and any observed depression in fatty acid β -oxidation rates is likely a result of a decline in function (292, 358, 367, 522, 606). Furthermore, studies using positron emission tomography and [^{11}C]palmitate imaging demonstrate that obese women and type 2 diabetic patients have an increased uptake and oxidation of fatty acids (229, 482). As a result, the preponderance of existing evidence

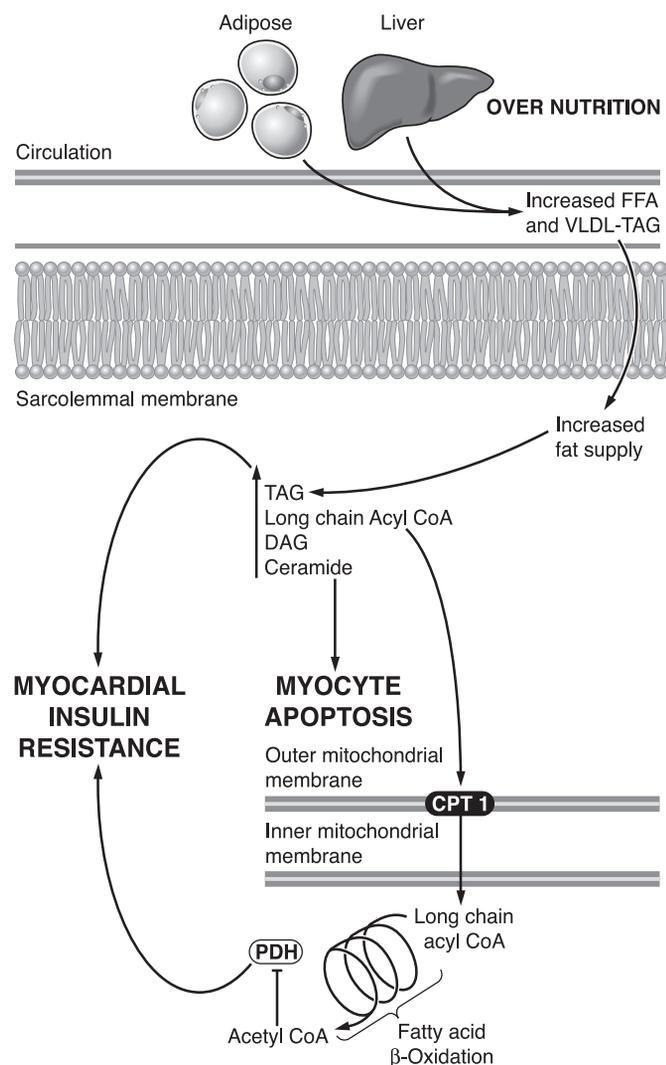


FIG. 6. The contribution of fatty acid β -oxidation to lipotoxicity and insulin resistance. In the setting of obesity and diabetes, increased circulating free fatty acid (FFA) and very-low-density lipoprotein-triacylglycerol (VLDL-TAG) concentrations result in an elevated lipid supply to the cardiac myocyte. This excessive lipid supply leads to the cytosolic accumulation of lipid metabolites such as TAG, long-chain acyl CoA, diacylglycerol (DAG), and ceramide. Increased levels of ceramide are believed to cause apoptosis of cardiac myocytes, which can result in contractile dysfunction, contributing to the cardiomyopathy observed in the setting of obesity and diabetes. In addition, accelerated rates of fatty acid β -oxidation lead to an increased production of acetyl CoA, which causes feedback inhibition of pyruvate dehydrogenase (PDH) and subsequent glucose oxidation, ultimately resulting in the development of myocardial insulin resistance.

suggests an increase in cardiac fatty acid β -oxidation occurs in obesity and insulin resistance, as opposed to an impaired fatty acid β -oxidation.

B. Transcriptional Alterations in Fatty Acid Metabolism and β -Oxidation

In obesity and diabetes, an increase in circulating FFA concentrations plays an important role in regulating

fatty acid metabolism due to increasing substrate supply. However, these fatty acids may also directly modify the expression of the enzymes of fatty acid metabolism, since fatty acids and their derivatives can serve as endogenous ligands for the PPAR family of nuclear receptors, with PPAR α and its coactivator PGC-1 being particularly important in the heart (60, 173, 190, 423) (Fig. 3). Activation of these nuclear receptors by fatty acids links the oxidative capacity of the heart to substrate supply (69). It appears that the early metabolic changes in obesity and diabetes occur independent of changes in PPAR α /PGC-1 and their downstream transcriptional targets (5, 16). However, chronic overnutrition and obesity appear to activate the PPAR α /PGC-1 signaling pathway, resulting in an increase in the mRNA for gene proteins that control fatty acid β -oxidation, including *m-cpt1*, *fatp1*, *facs1*, *cd36*, *ucp2*, and *ucp3* (5, 160). Increased PPAR α signaling was only observed in 15-wk-old *ob/ob* and *db/db* mice associated with increased FFAs (*db/db*) and TAG and development of hyperglycemia in both strains (60). Similarly, in streptozotocin-diabetic rats, PPAR α activation is only associated with a prolonged increase in plasma lipids, but not in acute diabetes (16). A number of studies observed greater expression of PPAR α , PGC-1, and target genes in both models of insulin resistance (131) and type 1 and 2 diabetes (41, 160, 573). Interestingly, cardiac specific overexpression of PPAR α in mice accelerates fatty acid β -oxidation and impairs the ability to utilize glucose, a phenotype similar to the diabetic heart (131, 160). In addition, PPAR α deficiency blunts the activation of fatty acid metabolic genes observed in insulin resistance and diabetes (41, 131).

Alterations in PPAR α and PGC-1 may also partially account for the suppression of glucose metabolism found in obesity and diabetes. PPAR α overexpressing mice have a significant reduction in glucose transporter 4 (GLUT4) mRNA and protein expression (160). In addition, PPAR α null mice are protected from the decrease in GLUT4 expression and glucose uptake observed during ischemia in wild-type mice subjected to streptozotocin-induced diabetes, high-fat diet, or a 24-h fast, all of which increase circulating FFA concentrations (460). PPAR α activation can also increase the transcription of *pdk4*, whose protein product can phosphorylate and inhibit the PDH complex, thus impairing glucose oxidation. Indeed, mice overexpressing PPAR α have increased PDK4 expression associated with decreased rates of glucose oxidation in the heart (241), while mice lacking PPAR α have increased rates of glucose oxidation (64, 548). Previous studies have demonstrated that increased PPAR α signaling accounts for an increase in PDK4 expression in a number of tissues (4, 238, 241, 247, 616–618). However, it has also been proposed that upregulation of PDK4 expression in heart and oxidative muscle may be due to a fatty acid-dependent, but PPAR α -independent mechanism (237, 239, 601).

In addition, mice deficient in PGC-1 also have a greater reliance on glucose oxidation (336).

C. Alterations in Circulating Fatty Acids and Adipokines and Their Regulation of Myocardial Fatty Acid β -Oxidation in the Setting of Obesity and Diabetes

Although the adipose tissue was once considered to be a passive energy reservoir, its role as an endocrine organ, by sensing changes in whole body energy metabolism and communicating these changes to the brain and other organs, is now well established (668). Adipose tissue synthesizes and secretes a number of hormones, such as the adipokines leptin, adiponectin, serum retinol-binding protein-4, resistin, and visfatin, as well as proinflammatory cytokines that include interleukin (IL)-6 and tumor necrosis factor- α (TNF- α) (668). Alterations in adipokine concentrations and signaling contribute to the metabolic phenotype in obesity and diabetes. Circulating concentrations of leptin (107), serum retinol-binding protein-4 (199, 478), resistin (611), and visfatin (177, 570) are positively correlated, and adiponectin (22, 103, 204) negatively correlated with fat adipose mass and accumulation in skeletal muscle and/or liver and insulin resistance. As discussed below, leptin and adiponectin can impact myocardial energy substrate metabolism. The role that serum retinol-binding protein-4 and visfatin play still remains to be investigated. Resistin may play a small role in myocardial metabolism by impairing glucose transport (202).

1. Regulation of myocardial fatty acid β -oxidation by leptin

Despite significant literature on the role of leptin in modulating whole body and skeletal muscle metabolism, there is limited direct evidence that leptin can modulate fatty acid metabolism in the heart. Treatment of HL-1 cardiac myocytes with leptin for 1 h significantly increases fatty acid β -oxidation, an effect associated with decreased intracellular lipid content, while prolonged exposure for 24 h decreases fatty acid β -oxidation leading to increased intramyocardial lipid content (457). Interestingly, this time course of leptin action parallels changes in AMPK and ACC phosphorylation, with an increase in phosphorylation at 1 h and no difference at 24 h. These observations are analogous to data obtained in skeletal muscle, where leptin-induced increases in fatty acid β -oxidation are attributed to the regulation of the AMPK/ACC/malonyl CoA signaling axis (405, 406, 623). Treatment of isolated working rat hearts with leptin also increases fatty acid β -oxidation of both exogenously and endogenously derived fatty acids, and is associated with a decrease in intramyocardial TAG stores (24). The greater reliance on

fatty acids as a source of oxidative metabolism is associated with an increase in $\dot{M}\dot{V}O_2$ and a decrease in cardiac efficiency (24). However, in contrast to what was observed in the HL-1 cardiac myocytes, the leptin-induced acceleration of fatty acid β -oxidation occurs independently of changes in cardiac AMPK or ACC, but may be explained by an increased activity of mitochondrial uncoupling proteins. As mentioned earlier, and in contrast to the effects of leptin on fatty acid β -oxidation rates in isolated hearts and cardiac myocytes, *ob/ob* and *db/db* mice also display increased myocardial fatty acid β -oxidation rates (60, 69, 387). However, this is most likely a secondary effect from a number of other alterations in these genetically modified animals, some of which include increased adiposity and plasma concentrations of FFAs and TAGs, as well as increased expression of a number of target genes in the PPAR α pathway (60). More specific detail with regard to the regulation of myocardial fatty acid β -oxidation rates in *ob/ob* and *db/db* mice is discussed in section IIIA.

2. Regulation of myocardial fatty acid β -oxidation by adiponectin

Similar to what is observed with leptin, adiponectin stimulates fatty acid β -oxidation in skeletal muscle via the AMPK/ACC/malonyl CoA signaling axis, although there is limited evidence that a similar mechanism occurs in the heart. Globular adiponectin (gAd) can potentially stimulate fatty acid β -oxidation in neonatal rat ventricular myocytes via an activation of AMPK and p38, leading to both an increase in CPT 1 activity and a decrease in malonyl CoA inhibition of CPT-1; however, actual rates of fatty acid β -oxidation have not been assessed (341). Incubation of neonatal rat ventricular myocytes with the hexameric/high-molecular-weight adiponectin also stimulates fatty acid β -oxidation via an AMPK-dependent signaling pathway through p38, and an AMPK-independent signaling pathway via p42/44 (414). In isolated working 1-day-old rabbit hearts, gAd significantly stimulates fatty acid β -oxidation via an AMPK/ACC-independent mechanism, while hexameric/high-molecular-weight adiponectin has no effect on fatty acid β -oxidation (445). gAd and hexameric/high-molecular-weight adiponectin are also unable to activate AMPK in isolated working mouse hearts (360). Recently, Palanivel et al. (458) have demonstrated that both gAd and adiponectin can stimulate fatty acid β -oxidation in neonatal cardiac myocytes, an effect associated with increased AMPK and ACC phosphorylation as well as decreased ACC activity (458). Interestingly, these authors also demonstrated that both gAd and adiponectin can stimulate fatty acid uptake via increased FATP1 expression (458).

Similar to what is observed with adiponectin treatment, conditioned medium from normal adipocytes can

increase palmitate uptake and oxidation, as well as glucose uptake and oxidation in neonatal cardiac myocytes (459). However, conditioned medium from streptozotocin diabetic rat adipocytes has an impaired ability to increase palmitate uptake, glucose uptake, AMPK phosphorylation, and glucose oxidation and actually inhibited palmitate oxidation and stimulated lactate production in cardiac myocytes (459). This study highlights the fact that adipokines should not be studied in isolation, but as physiologically relevant adipokine mixtures.

The significance of the adiponectin-induced changes in myocardial metabolism to obesity and diabetes remains unclear. Potentially the reduction in adiponectin associated with obesity may contribute to disease development in the heart due to the association of body mass index with a number of obesity-linked disorders. Interestingly, caloric restriction is associated with significantly elevated levels of adiponectin (134, 581, 725). Adiponectin protects the heart from ischemia/reperfusion injury *in vitro* (194) and *in vivo* (580, 634), as well as during the development of concentric cardiac hypertrophy in response to aortic constriction (579).

Taken together, there is limited evidence that leptin and adiponectin can modify myocardial fatty acid metabolism, but further studies are required to delineate the role of complex adipokine mixtures similar to those present during obesity and diabetes, on myocardial fatty acid metabolism and subsequent cardiac function and efficiency.

D. Contribution of Fatty Acid β -Oxidation to Insulin Resistance and Cardiac Pathology

Recent studies suggest that in the setting of obesity and type 2 diabetes, the heart has an impaired ability to oxidize fat and that the stimulation of fatty acid β -oxidation could benefit cardiac function by preventing the accumulation of intramyocardial lipids (573, 710, 712). Studies mainly in skeletal muscle have led to the postulation that the cytosolic accumulation of TAG, long-chain acyl CoA, DAG, and/or ceramide results from an impaired ability of the skeletal muscle to oxidize fatty acids in the setting of obesity and type 2 diabetes, and that these molecules subsequently impede insulin signaling via activation of the classical/novel protein kinase C signaling cascade (91, 92, 480, 588, 589, 718). Moreover, they have suggested that by enhancing the capacity of skeletal muscle to oxidize fatty acids, the cytosolic accumulation of these metabolites can be attenuated, thereby improving insulin signaling and glucose uptake, and ameliorating insulin resistance (91, 92, 480, 588, 589, 718). A caveat of the proposal that impaired fatty acid β -oxidation contributes to insulin resistance is that acceleration of fatty acid β -oxidation would decrease glucose oxidation via inhibi-

tion of PDH and phosphofructokinase, and thus reduce insulin-stimulated glucose metabolism based on the Randle cycle (495–497).

1. Myocardial insulin resistance

Insulin resistance is generally defined as a decrease in the action of insulin (stimulation of glucose uptake or oxidation, inhibition of lipolysis in adipocytes, or activation of downstream targets like Akt). Systemic insulin resistance, such as observed with diabetes, metabolic syndrome, obesity, or a sedentary life-style, generally elevates circulating FFA, TAG, glucose, and insulin. There are extensive data showing clear insulin resistance in obesity, type 2 diabetes, or physical inactivity in skeletal muscle, as seen in less insulin stimulation of glucose uptake, oxidation, or activation of Akt. On the other hand, there is growing evidence that there is little or no loss of insulin sensitivity in the heart in type 2 diabetes. Studies measuring the effects of hyperinsulinemia on glucose uptake in the human heart show either minor or no insulin resistance in patients with type 2 diabetes compared with nondiabetic control subjects (471, 655). This is particularly evident when plasma FFA levels are matched (260). Similar results have recently been reported in a genetic mouse model of type 2 diabetes (208), thus supporting the general concept that insulin responsiveness in the heart is relatively intact in type 2 diabetes (399). This is in clear contrast to skeletal muscle and adipose tissue, where insulin resistance results in elevated plasma glucose and FFA concentrations. The constant exposure of the heart to high FFA and glucose could exert toxic effects from the generation of noxious derivatives of glucose and lipid metabolism (87). Thus, while the heart may be less susceptible to insulin resistance than skeletal muscle, systemic insulin resistance may have a profound negative effect on the myocardium through the toxic effects of substrate overabundance (87).

Recent studies using mice deficient for ACC β (ACC β -/-) show reduced malonyl CoA levels and elevated myocardial fatty acid β -oxidation rates. However, despite an increase in myocardial fatty acid β -oxidation rates, ACC β -/- mice also have a significant increase in myocardial glucose oxidation rates and insulin stimulated 2-deoxyglucose uptake compared with their wild-type counterparts. Although these results suggest that accelerating fatty acid β -oxidation via inhibition of ACC may benefit the insulin-resistant heart in the setting of obesity and diabetes, the reported glucose oxidation rates were ~10- to 20-fold lower than the vast majority of rates reported in the literature. In addition, the authors observed an increase in both glucose oxidation and fatty acid β -oxidation rates, but no increase in oxygen consumption, presumably due to less oxidation of endogenous substrates. While these data are consistent with the

absence of the Randle cycle in skeletal muscle, numerous studies have clearly demonstrated that the Randle cycle is operative in cardiac muscle (348, 446, 609) and argue against accelerating fatty acid β -oxidation as a strategy to improve insulin signaling and function in the heart (360). Moreover, recent work from our laboratory has shown that mice deficient for MCD (MCD $-/-$) subjected to a chronic high-fat diet (60% energy intake from lard) have a marked preservation of insulin-stimulated glucose metabolism compared with wild-type mice subjected to the same high-fat diet (651). MCD $-/-$ mice have an elevation of malonyl CoA and subsequent reduction in the mitochondrial uptake of fatty acids, resulting in an increase in intramyocardial TAG. Despite this increase in TAG, there are no signs of cardiac dysfunction in MCD $-/-$ mice, suggesting that an inhibition of mitochondrial fatty acid uptake and oxidation do not adversely affect the heart in the setting of obesity and may actually have beneficial effects on insulin sensitivity. Further support for the lack of adverse cardiac effects of suppressed fatty acid β -oxidation comes from studies with long-term pharmacological inhibition of CPT 1, which found no cardiac dysfunction in normal or hypertensive rats despite elevated intramyocardial TAG levels (441). In contrast, deletion of ATGL (ATGL $-/-$) in mice results in a dramatic increase in intramyocardial TAG accumulation, which is associated with a decline in cardiac function (206). However, these mice show improved insulin sensitivity and glucose uptake in the heart. Although myocardial fatty acid β -oxidation rates were not measured in these studies, elevated respiratory exchange ratios and lower whole body oxygen consumption in ATGL $-/-$ mice suggest that fatty acid β -oxidation rates are indeed lower in these animals. Furthermore, it has recently been shown that PPAR α agonism in mice subjected to DIO improves postischemic recovery, which is associated with a reduction in plasma FFA levels and myocardial fatty acid β -oxidation rates (3). Although cardiac PPAR α agonism in isolation should increase fatty acid β -oxidation rates, peripheral PPAR α agonism results in a dramatic increase in hepatic fatty acid β -oxidation rates. Such an effect would likely reduce hepatic TAG synthesis, decreasing hepatic TAG secretion and subsequently decreasing fatty acid delivery to the heart, explaining why myocardial fatty acid β -oxidation rates were decreased in this particular study. Indeed, plasma TAG concentrations were also decreased, and PPAR α agonism in moderately overweight human subjects has also been recently shown to reduce plasma TAG concentrations with no effect on plasma FFA concentrations (515). In addition, treatment of hearts from *db/db* mice with high glucose-high insulin improves postischemic recovery, an effect associated with a reduction in myocardial fatty acid β -oxidation rates and a subsequent increase in glucose oxidation rates (207). Finally, treatment with the PPAR γ agonist rosiglitazone improves car-

diac efficiency in hearts from *db/db* mice, an effect once again associated with a reduction in plasma FFA levels and myocardial fatty acid β -oxidation rates, resulting in a subsequent increase in glucose oxidation rates (246).

2. Lipid-induced cardiac pathology

The intramyocardial accumulation of lipid metabolites (TAG and ceramide) in obesity and diabetes is also associated with cardiac pathology, which manifests with increased cardiac myocyte apoptosis, myocardial fibrosis, LV chamber expansion, contractile dysfunction, and impaired diastolic filling (156, 392, 555, 609, 648, 649, 700, 707, 724). While this general phenomenon has been observed in several genetic models in mice and rats, and has been broadly referred to as "cardiac lipotoxicity," it remains poorly defined and continues to lack a clinical equivalent condition. For example, obese Zucker diabetic rats develop cardiac dilatation and reduced contractility, effects that are associated with elevated intramyocardial TAG, ceramide, and increased DNA laddering, a marker of apoptosis (724). Interestingly, treatment of these animals with the PPAR γ agonist troglitazone suppressed plasma TAG levels and reduced intramyocardial TAG and ceramide accumulation, which was associated with a complete prevention of DNA laddering and restoration of cardiac function. Moreover, cardiac overexpression of FACS results in lipid accumulation, cardiac hypertrophy, gradual progression to LV dysfunction, and ultimately premature death (89). Cardiac overexpression of human lipoprotein lipase utilizing an anchoring sequence to localize the enzyme to the surface of cardiac myocytes causes LV chamber enlargement and impaired contractile function compared with wild-type counterparts (700).

It has been proposed that a downregulation of PPAR α and decreased expression of fatty acid β -oxidation enzymes causes intramyocardial lipid accumulation that contributes to the cardiac dysfunction that is sometimes observed with obesity, insulin resistance, and diabetes (87, 710, 712). This idea was supported by the observation that obese and type 2 diabetic patients with heart failure had a dramatic increase in intramyocardial lipid accumulation, which is attributed to impaired fatty acid β -oxidation due to a reduction in a number of PPAR α target gene transcripts (573). However, it is important to note that this study lacked an obese group without heart failure. Consuming a high-fat diet significantly increased body mass, intramyocardial TAG, and ceramide contents in rats with established infarct-induced heart failure, but did not negatively effect LV chamber dimensions, pressure, or mass (416), suggesting that lipid accumulation in the heart is not detrimental in heart failure.

Nonetheless, as discussed in the prior sections, studies in hearts from obese/insulin-resistant humans and rodents have not observed decreases in fatty acid β -oxida-

tion, but rather the opposite (26, 38, 73, 365, 387). It is also important to note that our recent work shows that subjecting mice to DIO for a 12-wk period does not result in any type of cardiac dysfunction, despite causing an accumulation of long-chain acyl CoA (651). We have also shown in a rat model of high-fat feeding that inhibition of CPT 1 via oxfenicine treatment leads to a significant elevation in intramyocardial TAG stores beyond that of high-fat feeding alone, but does not result in the development of cardiac hypertrophy or dysfunction (441). Furthermore, the inhibition of mitochondrial fatty acid uptake and fatty acid β -oxidation has been shown in a number of animal and human studies to prevent the progression of, or reverse the severity of, heart failure (37, 115, 172, 345, 524, 531–533, 643, 717) (see sect. IV D).

While the toxic effects of lipid accumulation in the heart can be demonstrated in rodent models, the clinical significance of these findings is not clear in patients with obesity, type 2 diabetes, and heart failure. Epidemiological studies demonstrate that obese individuals have a decrease in life expectancy, a greater risk for developing heart failure, and greater mortality from cardiovascular disease (167, 249, 286). However, once a patient is diagnosed with heart failure, there is a paradoxical reduction in the rate of mortality in obese compared with lean patients (119, 242, 329, 330). These observations are complicated by findings demonstrating that cachexia is a positive predictor of mortality in heart failure and that weight loss is strongly associated with poor outcome (20, 119, 609). Furthermore, strong evidence is lacking to suggest that obese individuals with chronically elevated plasma TAG or FFAs have elevated intramyocardial lipid accumulation or lipid-induced cardiac pathology (360). In a small study, heart failure patients with elevated intramyocardial TAG stores had more severe changes in the mRNA levels of genes known to be altered in severe heart failure (i.e., myosin heavy chain- β), yet there was no evidence of worse clinical heart failure or contractile dysfunction in this subgroup (573). Thus further research is required to determine the true significance of lipid accumulation and the development of lipotoxicity in the heart in both animal and human studies.

E. Cardiac Efficiency in Obesity and Diabetes

In obesity and diabetes, there is an increase in $M\dot{V}O_2$ and a decrease in cardiac efficiency, which has been observed in both animals (54, 55, 60, 244, 387) and humans (482, 483). This is not surprising, as oxidation of fatty acids is less oxygen efficient than glucose as an energy source (see sect. II J). In streptozotocin-diabetic mouse hearts, a 57% increase in unloaded $M\dot{V}O_2$ is seen, which occurs independent of changes in circulating fatty acids, and a 86% increase in unloaded $M\dot{V}O_2$ is seen in

db/db mice paired with a decrease in contractile efficiency at high concentrations of fatty acids (244). Although a similar decrease in cardiac efficiency is observed in a number of studies, the mechanism by which efficiency is impaired differs. How et al. (244) demonstrated only a slight impairment in cardiac output in *db/db* hearts and no impairment in hearts from streptozotocin-treated mice, although other studies have demonstrated a significant reduction in cardiac work in addition to increased myocardial oxygen consumption (1, 54, 60, 68, 193, 387). Despite the differences in mechanisms, these studies support the concept that cardiac efficiency is reduced in diabetic mouse hearts. In contrast, some studies have reported normal cardiac efficiency in the Zucker diabetic fatty rat despite elevated rates of fatty acid β -oxidation (526, 590, 673).

Another potential mechanism for cardiac inefficiency in obesity and diabetes is oxygen wasting due to energy use for noncontractile purposes. Mitochondrial dysfunction has been identified in a number of models of obesity and diabetes, suggesting that compensatory mechanisms eventually become maladaptive (577, 578, 645, 646). Indeed, even though PGC-1 and its downstream target genes that regulate fatty acid β -oxidation are increased in *db/db* mice, there is not a concomitant increase in the genes of oxidative phosphorylation (5). In addition, in the *ob/ob* mouse, protein contents of complexes I, III, and V are reduced, and isolated mitochondria have a reduced oxidative capacity (5). Mitochondrial uncoupling, as evidenced by reduced P/O ratios and measures of proton leak kinetics, have demonstrated increases in oxygen consumption as well as increases in fatty acid β -oxidation in a number of models of obesity and diabetes (55, 131). A potential mechanism leading to this mitochondrial uncoupling is either the increase in activity and/or expression of uncoupling proteins, particularly UCP3, in hearts from obese and diabetic animals (55, 60, 231, 422, 423, 713). In addition to uncoupling proteins, the ANT has been demonstrated to mediate fatty acid induced uncoupling. ANT1, the major isoform expressed in the adult heart, is involved in the transport of fatty acid anions out of the mitochondria into the cytosol, a process that is inhibited by carboxyatractyloside (18, 19, 129, 560, 593, 691).

In addition to mitochondrial uncoupling, oxygen can also be utilized for other noncontractile processes, including fatty acid esterification and the production of reactive oxygen species (407, 664, 665). This mitochondrial dysfunction may partially account for the cardiac phenotype of obesity and diabetes due to increased production of ROS and subsequent oxidative stress (55, 175, 342, 553, 577, 662, 705, 706). Cardiac efficiency may also be reduced by flux through futile cycles that waste ATP, which may include the cytosolic and mitochondrial thioesterases and the FACS reactions; indeed, cardiac expression of cytosolic thioesterase 1 and MTE 1 are elevated following

streptozotocin-induced diabetes and high-fat feeding (132, 187, 235, 296).

F. Functional Consequences of Altered Fatty Acid Metabolism in Obesity

It is well established that obese individuals are at an increased risk of developing cardiovascular disease (249, 280, 503). While patients with obesity have an increased risk for ischemic heart disease, a significant proportion of these patients will develop heart failure independent of ischemia (13, 694). A number of changes to the myocardium contribute to the dysfunction observed in the patient with obesity, such as altered sarcoplasmic reticulum calcium handling (52, 477, 484), but we will focus on the contribution of altered fatty acid β -oxidation to these processes.

A number of studies in both humans and animals have suggested a link between excessive rates of fatty acid β -oxidation in the heart and alterations in cardiac function. For instance, healthy patients placed on a 3-day very-low-calorie diet (VLCD) to induce elevations in plasma fatty acid levels have an increase in intramyocardial TAG stores, which is associated with a reduction in the deceleration of the early filling phase of the LV, an index of diastolic function (659). Treatment of patients with type 2 diabetes on a 3-day VLCD with the antilipolytic agent acipimox was able to reduce intramyocardial TAG stores and restore diastolic function (217). Unfortunately, these studies did not investigate what effect this protocol had on levels of other lipid metabolites and rates of myocardial fatty acid β -oxidation. A prolonged VLCD results in a dose-dependent increase in intramyocardial TAG stores and subsequent decline in diastolic function in healthy patients (218). In addition, a prolonged VLCD in obese patients with type 2 diabetes showed a decrease in both body mass index and intramyocardial TAG stores, while diastolic function was restored (216). Similarly, healthy people who subject themselves to chronic food restriction have significantly improved LV indexes of diastolic function compared with age-matched controls (403). However, one must use caution when interpreting the results of such findings, as cachexia is associated with a poorer outcome in patients with heart failure (20, 119, 609).

Cardiac-specific overexpression of FATP1 results in an excessive fatty acid supply to the heart that is not accompanied by a parallel increase in fatty acid metabolism, and no apparent systolic dysfunction, but predominant diastolic dysfunction as seen with the increase in the E/A ratio and decrease in the deceleration filling time of the LV (90). In addition, mice with a cardiac-specific overexpression of PPAR α also demonstrate systolic dysfunction via echocardiography, which was associated with an elevation in myocardial fatty acid β -oxidation

rates (160). Because these mice have a cardiac phenotype that is similar to what is observed in type 2 diabetes, one cannot discern whether it is the increase in fatty acid β -oxidation rates or some other effect of PPAR α that is responsible for the development of systolic dysfunction in these animals. Finally, mice with a cardiac-specific overexpression of FACS develop cardiac hypertrophy with severe systolic dysfunction and premature death due to heart failure (89).

G. Functional Consequences of Altered Fatty Acid Metabolism in Diabetes

In parallel with the setting of obesity, diabetic individuals are at an increased risk of developing cardiovascular disease (249, 280, 503) and can develop heart failure independent of ischemia (155, 404, 503, 505, 522, 523). The heart failure may be accompanied without a reduction in LV ejection fraction, or systolic dysfunction may be apparent in the form of a reduced LV ejection fraction and ejection time, which may occur even in young diabetics (9, 503, 552). Diastolic dysfunction is also observed with elevations in LV end-diastolic pressure, which impairs diastolic filling of the ventricle and affects compliance (503, 504).

As the pathological consequences of intramyocardial accumulation of lipids have been proposed to contribute to the development of cardiomyopathy (see sect. III D), it has been postulated that an impairment in cardiac fatty acid β -oxidation plays a major role with its progression in type 2 diabetes (88, 303, 360, 571, 609, 627, 702). Interestingly, numerous studies in rodent models of diabetes also report decrements in systolic function via echocardiography, such as studies in Zucker diabetic fatty rats and in *db/db* mice (569, 710, 724), and, as mentioned previously, hearts from *db/db* mice actually exhibit increased rates of fatty acid β -oxidation, reduced cardiac efficiency, and eventual contractile dysfunction (2, 60, 66, 69, 207, 245, 246, 387). Hearts from *db/db* mice that overexpress the GLUT4 transporter have a normalization of myocardial fatty acid β -oxidation rates and a restoration of glucose utilization and function (38). In addition, mice with a cardiac overexpression of PPAR α have a phenotype mimicking that seen in type 2 diabetes, which is associated with elevated fatty acid β -oxidation rates, systolic dysfunction, and ventricular hypertrophy as determined by echocardiography (160). If these mice are placed on a high-fat diet enriched with long-chain fatty acids, they developed worse cardiac dysfunction, but not when fed medium-chain fatty acids (156). This may be due to increased cardiac myocyte apoptosis from long-chain fatty acid-derived ceramide, or inhibited mitochondrial uptake of long-chain fatty acids through CPT 1, resulting in increased delivery of long-chain fatty acids to the peroxi-

somes for oxidation and subsequent production of toxic hydrogen peroxide. As medium-chain fatty acids do not require CPT 1 for access to the mitochondrial β -oxidative machinery, they would bypass these potential toxic by-product producing pathways. Cardiac overexpression of PPAR γ in mice yielded a similar effect, as fatty acid uptake, storage, and oxidation enzymes were all increased concomitantly with intramyocardial stores of TAG and ceramide, which was associated with a reduction in contractile function (598). Unfortunately, direct measurements of myocardial fatty acid β -oxidation and glucose oxidation were not assessed. Interestingly, if de novo ceramide production was prevented via inhibition of serine palmitoyltransferase, elevated fatty acid β -oxidation rates were normalized with a complete restoration of glucose oxidation rates in mice with a cardiac overexpression of glycosylphosphatidylinositol-anchored human LPL (469). These metabolic changes were also associated with an improvement in contractile function. Cardiac overexpression of either FACS or FATP1 leads to the development of a lipotoxic cardiomyopathy that is associated with elevations in intramyocardial lipid accumulation (88, 89).

Accelerated fatty acid and/or ketone body oxidation and a reciprocal decrease in glucose oxidation are also believed to play a role in the initial processes that lead to a decline in cardiac function in type 1 diabetics (522). As such, in rodent models of type 1 diabetes, inhibition of fatty acid β -oxidation is associated with improvements in LV contractile performance. Streptozotocin-induced diabetes in rats results in a reduction in cardiac function in isolated working hearts 30 days postinjection (656, 657). Perfusion of these hearts with the CPT 1 inhibitor methyl palloxirate reduces the diabetes-induced elevation in intramyocardial long-chain acylcarnitines and restores cardiac function (628). Furthermore, inhibition of CPT 1 with etomoxir in streptozotocin diabetic rats leads to a doubling of myocardial glucose oxidation rates and restores the decline in cardiac function (670). Interestingly, overcoming fatty acid-induced inhibition of glucose oxidation via direct stimulation of PDH with DCA restores contractile performance in hearts from rats with streptozotocin-induced diabetes (434).

Aging is also associated with the development of insulin resistance and cardiomyopathy (303, 319, 479), where in both cases, once again, an impairment in fatty acid β -oxidation has been proposed to contribute to the development of both diseases (285, 479, 514, 594). On the contrary, FAT/CD36-deficient (CD36 $^{-/-}$) mice fed regular chow have an improved basal insulin sensitivity and are protected from high-fat diet-induced insulin resistance (210). Furthermore, although they have a marked reduction in cardiac fatty acid β -oxidation rates, likely through the Randle cycle, they have a compensatory increase in glucose oxidation (311). Although aging is asso-

ciated with the development of insulin resistance and a steady decline in cardiac function, hearts from aged CD36 $^{-/-}$ mice do not fail at elevated work loads compared with wild-type counterparts, which was due to a preservation of cardiac glucose oxidation rates (303). Recently, it has also been demonstrated that chronic high-fat feeding of rats leads to the development of insulin resistance and a diabetic cardiomyopathy, which was associated with the relocation of FAT/CD36 into the sarcolemmal membrane and enhanced rates of long-chain fatty acid uptake and intramyocardial TAG content (455). Interestingly, deletion of FAT/CD36 in mice with a cardiac overexpression of PPAR α rescues the lipotoxic cardiomyopathy of these animals, which is associated with a reduction in intramyocardial TAG content, a restoration of myocardial glucose oxidation rates, and a trend to a reduction in fatty acid β -oxidation rates (702).

In summary, it does appear from numerous studies that lipid accumulation from an excessive fatty acid supply contributes to the development of cardiomyopathy in rodent models of obesity and diabetes. However, an impaired ability of the heart to oxidize fatty acids does not appear to play a significant role in this process, as interventions that either normalize or reduce myocardial fatty acid β -oxidation rates appear to have beneficial effects on diabetic cardiomyopathy in animals and humans.

IV. MYOCARDIAL FATTY ACID METABOLISM IN HEART FAILURE

Heart failure can have a profound impact on cardiac fatty acid metabolism via both systemic and cardiac-specific mechanisms (see Ref. 609 for review of cardiac energy metabolism in heart failure). However, the effects of heart failure on fatty acid metabolism are complex, due in large part to the complexity of heart failure itself. Heart failure is not a disease but rather a complex clinical syndrome that is generally defined as an impaired ability of the ventricle to fill with and eject blood (251). The etiology of heart failure is complex, but is broadly divided into two main categories: 1) ischemic heart failure (patients with a history of coronary artery disease and/or myocardial infarction), and 2) nonischemic idiopathic heart failure. Most heart failure patients have a history of hypertension (~75%) and LV hypertrophy (198). Approximately 50–60% of heart failure patients have an enlarged LV chamber and reduced ejection fraction, while 40–50% have a normal LV volume and ejection fraction (43, 456).

A. Systemic Effects of Heart Failure on Myocardial Fatty Acid Metabolism

Assessment of myocardial fatty acid metabolism in heart failure is confounded by changes in the circulating

concentration of FFAs and ketone bodies (β -hydroxybutyrate and acetoacetate), as well as by the fact that ~30% of heart failure patients in developed countries have diabetes, which in itself can have dramatic effects on fatty acid metabolism (as discussed in sect. III). With regard to circulating substrate supply, studies by Lommi and co-workers (352, 353) found a higher rate of plasma FFA turnover and elevated FFA concentration in heart failure patients compared with controls, which exposes the heart to a greater FFA load and could increase myocardial FFA uptake and β -oxidation through simple mass action (688). Circulating FFA levels can also increase in the setting of acute heart failure, where the catecholamine surge during this period can increase circulating fatty acid levels (352, 353, 464), which can lead to an increase in fatty acid β -oxidation in the heart. In contrast, there can also be increases in ketone bodies in heart failure patients, which is associated with the severity of heart failure (351–353). Relatively modest elevations in ketone bodies inhibit myocardial fatty acid uptake and oxidation in humans, pigs, and isolated cardiac myocytes (82, 168, 226, 322, 346, 607, 661), suggesting that in heart failure a normal or low uptake of fatty acids could be partially explained by high circulating concentrations of ketone bodies. Data on cardiac ketone body uptake and/or oxidation in heart failure has not been reported. In vivo studies on the effects of heart failure should take into consideration the impact these differences in circulating FFA and ketone bodies have on myocardial substrate metabolism (e.g., using regression analysis to separate myocardial effects from substrate delivery).

B. Direct and Indirect Measurements of Fatty Acid β -Oxidation in Heart Failure

Few studies have directly measured myocardial fatty acid metabolism in heart failure patients or large-animal models. There are two reports of direct invasive measurement of myocardial fatty acid metabolism in heart failure patients. Paolisso et al. (464) measured the net extraction of FFA by the myocardium using simultaneous arterial and coronary sinus sampling in patients with moderately severe heart failure [New York Heart Association (NYHA) Class II and III] and in age-matched healthy individuals. The rate of fatty acid β -oxidation was estimated from the transmucosal respiratory quotient. Heart failure patients had elevated plasma norepinephrine and insulin as well as a 50% increase in FFA concentrations. FFA uptake and the estimated fatty acid β -oxidation rates were ~40% higher in heart failure patients than in controls, despite no difference in coronary blood flow or the rate of cardiac energy expenditure. More recently, direct measurements were made of FFA oxidation in patients with dilated cardiomyopathy using an infusion of [3 H]oleate tracer and

arterial and coronary sinus sampling to assess oxidation to $^3\text{H}_2\text{O}$ (429). Arterial FFA concentration was not different between groups. Compared with control patients, heart failure patients have reduced uptake and oxidation of FFA both in absolute terms and when normalized to myocardial oxygen consumption. FFA uptake was negatively correlated with LV chamber enlargement ($r = -0.81$), and lower FFA uptake and β -oxidation persisted during and after acute pacing stress. These results show that in dilated cardiomyopathy there is a preferential decrease in FFA β -oxidation, which contrasts sharply with the study by Paolisso et al. (464) described above.

A number of indirect measurements of myocardial fatty acid metabolism have been performed in heart failure patients using noninvasive imaging with radiolabeled fatty acid tracers. Measurements with positron emission tomography (PET) using [^{18}F]fluoro-6-thia-heptadecanoic acid and [^{18}F]fluoro-deoxyglucose to estimate fatty acid and glucose uptake in congestive heart failure patients found fatty acid uptake to be higher and glucose uptake lower than published literature values from healthy people (635). A limitation of this study was the lack of a contemporary control group. In contrast, Davila-Roman et al. (118) used PET to assess myocardial blood flow, energy expenditure, and fatty acid and glucose metabolism using ^{15}O -labeled water and ^{11}C -labeled acetate, palmitate, and glucose tracers in patients with nonischemic idiopathic dilated cardiomyopathy (LV hypertrophy and an ejection fraction of 27%) (118). Compared with healthy volunteers, there were no differences in arterial blood pressure, plasma FFA or insulin levels, or myocardial blood flow and oxygen consumption. On the other hand, calculated fatty acid uptake and β -oxidation were decreased by ~40%, and glucose uptake was doubled in heart failure patients compared with controls. Studies using the radiolabeled fatty acid analog ^{123}I - β -methyl-iodophenylpentadecanoic acid (BMIPP) assessed regional tracer kinetics and contractile function and found reduced tracer retention in dyskinetic segments in patients with severe idiopathic dilated cardiomyopathy, consistent with impaired fatty acid utilization in the failing myocardium (704). Taken together, while there is variability among these clinical investigations, in general the data support the concept that in the absence of a significant elevation in plasma FFA concentrations, there is a significant decrease in the rate of fatty acid β -oxidation in advanced heart failure both in absolute terms and as a fraction of myocardial oxygen consumption. These findings are consistent with the data presented below showing a decrease in the myocardial capacity for fatty acid β -oxidation in animal models of heart failure.

Results from animal models of heart failure generally support the concept of decreased fatty acid β -oxidation in heart failure. Studies using the canine tachycardia model of heart failure show a progressive fall in fatty acid uptake

and oxidation measured either directly (435, 454, 492, 502) or with BMIPP (284). On the other hand, dogs with moderate severity microembolization-induced heart failure showed normal myocardial FFA and glucose uptake and oxidation (80), despite severe impairment in mitochondrial respiratory capacity and function (525, 575). Results from the rat chronic coronary ligation model show that 8 wk after infarction, there is clear LV dysfunction but normal myocardial oxygen consumption and palmitate oxidation in isolated hearts perfused with buffer containing erythrocytes (509). Rats studied 6 mo after infarction (228) showed a decrease in cardiac palmitate oxidation measured without erythrocytes in the perfusate; however, myocardial oxygen consumption was not measured and may have been lower. A similar decrease in FFA oxidation was observed in rats with LV hypertrophy and contractile dysfunction induced by either aortic banding (12), volume overload caused by an aortocaval fistula (95, 149, 150), or chronic spontaneous hypertension (93). Thus, in rodent models of heart failure, there is a decrease in the rate of myocardial fatty acid oxidation.

C. Alterations in Transcriptional Control of Fatty Acid β -Oxidation Enzymes in Heart Failure

There is extensive evidence to suggest impaired mitochondrial function, including a decreased expression and activity of proteins involved in cardiac fatty acid uptake and oxidation in advanced heart failure. Patient studies (536) found decreased mRNA and protein expression for selected enzymes of the fatty acid β -oxidation pathway in myocardial samples from explanted hearts from transplant recipients compared with nonfailing donors. Specifically, mRNA levels were reduced for the β -oxidation enzymes long-chain acyl CoA dehydrogenase and MCAD, and protein levels of MCAD, with no change in the mRNA encoding the glycolytic enzyme glyceraldehyde phosphate dehydrogenase. Martin et al. (386) found no difference in the activity of CPT 1 but a decrease in CPT 2 activity in LV myocardium from heart failure patients undergoing transplantation compared with nonfailing donor hearts. The tissue concentration of long-chain acylcarnitine was also elevated fourfold, and free carnitine decreased by 50%, which is consistent with reduced CPT 2 activity. Dogs with end-stage tachycardia-induced heart failure also show a downregulation of fatty acid β -oxidation enzymes, including a decrease in the activity of CPT 1 that corresponded with a comparable decrease in fatty acid β -oxidation in vivo (337, 454). On the other hand, dogs with microembolization-induced heart failure had normal CPT 1 or MCAD activities (80, 462, 525), but had a 40–50% decrease in mitochondrial state III respiration with both lipid and nonlipid substrates (525, 575,

576), suggesting impaired function of the ETC and not a selective decrease in fatty acid β -oxidation. Rodents with infarct-induced heart failure (415, 416, 509, 527) or arterial pressure overload (85, 86, 443, 536) generally show a modest decrease in the activity and protein expression of mitochondrial fatty acid β -oxidation enzymes. Isolated mitochondria from rats with heart failure caused by an aortocaval fistula have suppressed respiration with lipid substrates, but not with glutamate or malate, suggesting selective impairment of the capacity for fatty acid β -oxidation in this model (149).

In general, the heart failure-induced downregulation of mRNA for genes encoding proteins involved in fatty acid uptake and β -oxidation is far more pronounced than effects on protein expression and enzymatic activity (120, 337, 345, 415, 416, 443, 476, 527). Myocardial levels of mRNA for key enzymes of the fatty acid β -oxidation pathway, and also carbohydrate metabolism (glucose transporters, glyceraldehyde phosphate dehydrogenase, and pyruvate dehydrogenase), are decreased in dogs with end-stage heart failure compared with normal myocardium (337). Thus heart failure appears to suppress the transcription of a broad array of metabolic enzymes and does not selectively downregulate the expression of fatty acid β -oxidation enzymes, nor upregulate glycolysis or pyruvate oxidation. Recent analysis of DNA microarray data from heart failure patients found downregulation of PGC-1 α target genes involved in fatty acid metabolism (591). In addition, there was a subset of genes controlled by the PGC-1 α regulatory partner, estrogen-related receptor α (ERR α), which were also downregulated in heart failure. The changes in PGC-1 α and ERR α target genes were positively correlated with LV ejection fraction, suggesting that both PGC-1 α and ERR α may regulate the decrease in the mRNA for genes encoding proteins in the mitochondrial fatty acid metabolism pathway in human heart failure.

The mechanisms responsible for the heart failure-induced decrease in the expression and activity of proteins involved in myocardial fatty acid β -oxidation is not well understood but appears to be partially the result of reduced activation of gene expression by the PPAR α pathway. As discussed in section 1, PPAR α is a ligand-activated nuclear receptor that forms a heterodimer with the retinoic acid X receptor α (RXR α) and PGC-1 α (40). When stimulated by fatty acids, the PPAR α /RXR α /PGC-1 α complex binds to specific PPREs located within promoter regions of genes encoding proteins involved in fatty acid uptake and oxidation, as well as inhibition of pyruvate oxidation (252). The activity of PPAR α decreases in response to hypertrophic growth in vitro (32, 33), as reflected by a fall in the mRNA levels of genes regulated by PPAR α . In vivo studies showed similar effects with advanced pressure overload-induced cardiac hypertrophy (32, 442) and with heart failure in mouse, rat, and dog

models (85, 86, 121, 318, 337, 345, 415–417, 476). The mechanism for this effect is unclear, but unlikely to be due to less ligand stimulation by fatty acids, as fatty acid levels increase in heart failure (352, 353). There is some evidence that there is a decrease in the protein levels of PPAR α and RXR α in heart failure. PPAR α protein levels were decreased by 54% in LV biopsies from five end-stage heart failure patients compared with control donor hearts (282). The expression of RXR α has not been reported in heart failure patients; however, studies in the canine tachycardia and rat hypertension-induced models of heart failure found a significant decrease in RXR α protein levels without a change in PPAR α (443, 454) or PGC1 α (337). Rats with myocardial infarct-induced heart failure showed a significant reduction in the mRNA for both PPAR α and RXR α , but no change in the expression of these proteins (415). One likely possibility is that heart failure disrupts the formation of the PPAR α /RXR α /PGC-1 α complex in the nucleus and/or binding to PPAR response elements, as suggested by the marked downregulation of the PPAR α /RXR α complex in isolated cardiac nuclei from rats with hypertension-induced cardiac hypertrophy, despite no change in total protein levels for PPAR α and RXR α (279). In a transgenic mouse model of heart failure induced by targeted cardiac overexpression of angiotensinogen, there is a decrease in the mRNA and protein levels of PPAR α and its downstream targets CPT 1 and MCAD, particularly in mice with more severe heart failure as evidenced by pulmonary congestion (476). Despite a 90% decrease in protein expression for PPAR α , CPT 1, and MCAD in mice with severe heart failure there is only a modest 25% decrease in the rate of palmitate oxidation in perfused working hearts.

The role of the decrease in the activity of PPARs and the capacity for myocardial fatty acid metabolism in the progression of heart failure has recently been investigated using selective agonists of PPAR α , β/δ , and γ in animal models of chronic heart failure. Pharmacological activation of PPAR α was first shown to upregulate PPAR α -regulated genes and worsen *ex vivo* LV function in rats subjected to severe aortic hypertension (711). A subsequent study examining long-term treatment with fenofibrate in rats with established infarct-induced heart failure found a 50% increase in the activity and protein expression of MCAD, but no effect on LV function or chamber volume (416). Similar findings were found in a dog tachycardia model of heart failure (318). On the other hand, in the pig tachycardia model, the PPAR α agonist fenofibrate partially prevented the deterioration in LV function (57). Thus it appears that pharmacologically preventing the downregulation of PPAR α and activity of its target genes has little effect on the progression of heart failure. Taken together, there is not strong evidence to support the concept that deactivation of PPAR α and decreases in mRNA levels of genes encoding proteins involved in fatty

acid metabolism contribute to the development or progression of heart failure.

Less is known about the role of PPAR β/δ in the failing heart. Mice with cardiac-specific deletion of PPAR β/δ have decreased expression of key fatty acid β -oxidation genes and exhibited intramyocardial lipid accumulation and cardiomyopathy (83). In contrast, mice with cardiac overexpression of PPAR β/δ are strikingly different from PPAR α overexpressing mice, as demonstrated by accelerated glucose use and no lipid accumulation or cardiac dysfunction (61). Treatment of rats with infarct-induced heart failure with the PPAR β/δ agonist GW610742X switched substrate oxidation from fatty acids to carbohydrate but had little effect on the mRNA expression of fatty acid metabolism enzymes and did not affect LV chamber enlargement or progression of heart failure (272). Treatment with a PPAR γ agonist had little effect on cardiac structure or function in dogs with established microembolization-induced heart failure (624), and increased mortality in rats with infarct-induced heart failure (378). The effects of a PPAR γ agonist on cardiac fat metabolism in heart failure have not been reported.

D. Contribution of Altered Fatty Acid β -Oxidation to Contractile Dysfunction in Heart Failure

As noted above, current evidence suggests that the myocardial capacity for fatty acid β -oxidation is relatively normal during the early development of heart failure, while there is a clear decrease in fatty acid β -oxidation capacity in the more advanced stages. Since fatty acids are a less efficient fuel than carbohydrates, this has been viewed by some investigators to be a positive adaptation. Thus it has been proposed that pharmacological inhibition of fatty acid β -oxidation would be an effective treatment for heart failure (see Ref. 609 for review). Results of experiments in animal models of heart failure and small clinical trials suggest that long-term treatment with the CPT 1 inhibitors perhexiline (333), etomoxir (642, 643), or oxfenicine (345), or the direct inhibitor of the fatty acid β -oxidation trimetazidine (37, 115, 171, 647, 666) are indeed beneficial. The mechanism(s) for these beneficial effects is not clear, but could be due to improved ATP formation due to better mitochondrial coupling and decreased fatty acid β -oxidation, resulting in a higher rate of ATP production at a given rate of myocardial oxygen consumption (higher P/O ratio) (see sect. IIJ).

Our understanding of the underlying mechanisms responsible for the beneficial effects of CPT 1 inhibitors and direct inhibitors of fatty acid β -oxidation in heart failure is limited by a poor understanding of the fundamental effects of heart failure on mitochondrial structure, function, and metabolism of fatty acids. Mitochondria in advanced heart failure are characterized by a lower capacity for

respiration and oxidative phosphorylation (see Refs. 432, 609 for review). In general, the literature supports the concept that the main defects in cardiac mitochondria in heart failure are not in generation of reducing equivalents (NADH and FADH₂), but rather in the respiratory apparatus and oxidative phosphorylation (432, 609). An array of defects in ETC complexes have been noted in various forms of heart failure, with no consistency (432, 609). A recent comprehensive examination of cardiac mitochondrial function dogs with coronary microembolization induced heart failure found decreases of ~40%-50% in ADP-stimulated respiration that was not relieved by an uncoupler (525). Maximal respiration was similarly decreased with palmitoyl CoA, palmitoylcarnitine, glutamate, pyruvate, or succinate plus rotenone as substrates, or with artificial electron donors. While this suggests a defect in oxidative phosphorylation within the ETC, the individual activities of ETC complexes were normal, as were the activities of TCA cycle enzymes (80, 462, 525). The amount of the supercomplexes consisting of complex I/complex III dimer/complex IV, the major form of the respirasome essential for oxidative phosphorylation (130, 556, 557, 720, 721), was decreased, suggesting that the mitochondrial defect in heart failure lies in the supermolecular assembly rather than in the individual components of the ETC (180, 525). It is not known how agents that affect fatty acid β -oxidation and have had favorable results in small clinical trials in heart failure patients (trimetazidine and perhexiline) affect assembly and function of the ETC.

As discussed in section VI, partial inhibition of myocardial fatty acid β -oxidation during acute ischemia or postischemia reperfusion can increase pyruvate oxidation and decrease lactate production, which is associated with improved contractile function and clinical improvement during exercise or β -adrenergic agonist-induced stress in patients with chronic stable angina (320, 602). This mechanism is unlikely to play a role in the improvement in LV function in patients and animals with heart failure, as evidenced by the relatively normal myocardial lactate uptake during pacing stress (429) or exercise (17) in heart failure patients. Further support for this concept comes from studies in pigs with ischemic heart failure induced by chronic coronary artery constriction, where there is no myocardial lactate production during intense β -adrenergic stimulation despite a chronic reduction in contractile function and $\dot{M}\dot{V}O_2$ at rest (152).

Another effect of long-term treatment with a CPT 1 inhibitor is an increase in the mRNA levels for genes that are regulated by PPAR α and other genes that are known to be downregulated in heart failure (345, 441, 533). This effect has been shown to prevent the decrease in protein expression and activity of fatty acid β -oxidation enzymes in advanced end-stage heart failure in dogs (345), and is presumably mediated by an increase in the cytosolic concentration of the endogenous fatty acid ligands for PPAR α

which occurs with CPT 1 inhibition (343). Oxfenicine-treated dogs with tachycardia-induced heart failure had attenuated and delayed LV remodeling compared with untreated animals, and maintained activity of citrate synthase, a TCA cycle enzyme that is not regulated by PPAR α , suggesting that CPT 1 inhibition may preserve or restore mitochondria function in heart failure.

V. ALTERATIONS IN FATTY ACID METABOLISM IN THE SETTING OF ISCHEMIC HEART DISEASE

Myocardial ischemia occurs when coronary blood flow is inadequate, and hence, the oxygen supply to the myocardium is not sufficient to meet oxygen demand. Due to the heart's high demand for energy and thus high rates of oxidative metabolism utilized to drive cardiac contraction, the manifestations of myocardial ischemia are dependent on the nature and severity of the ischemic episode and the subsequent reestablishment of flow (reperfusion). Ischemic heart diseases ranging from angina pectoris to acute myocardial infarction and heart failure impact both cardiac metabolism and function. In the normal heart, energy metabolism and cardiac function are exquisitely matched; however, ischemia elicits disturbances in the balance between fatty acid and glucose oxidation. The predominance of fatty acid β -oxidation as a source for ATP generation at the expense of glucose oxidation during reperfusion following ischemia negatively influences cardiac efficiency (see sect. IIK) and function in isolated perfused hearts. Recent data in humans also support this concept, because use of a comprehensive metabolomics approach revealed that fatty acid extraction persisted as the major fuel substrate contributing to myocardial ATP requirements in patients with coronary artery disease after reperfusion following cardiac surgery versus control patients (644). Thus optimizing energy substrate metabolism such that the efficiency of both generating and utilizing ATP is maximized is a useful therapeutic intervention in various manifestations of ischemic heart disease (see sect. VI).

The consequences of myocardial ischemia are numerous, and metabolic perturbations with regard to the availability of circulating energy substrates, as well as the regulation of energy substrate metabolism, specifically fatty acids and fatty acid β -oxidation, are important factors underlying some of these consequences. Important factors regulating fatty acid β -oxidation include the concentration of circulating plasma FFAs and the intracellular content of malonyl CoA, which itself is primarily regulated by the AMPK-ACC-MCD axis (142, 653, 654) (see sect. IIE).

A. Ischemia-Induced Alterations in Plasma FFA Concentrations

The concentration of circulating FFAs is influenced by a variety of factors such as prandial and hormonal state. Fasting increases circulating plasma FFA concentrations, whereas there is a decrease in circulating plasma FFA concentrations in the postprandial state due to the antilipolytic effects of insulin (496, 497). Ischemia rapidly increases catecholamine discharge, be it in response to myocardial ischemia arising from underlying pathophysiological alterations or in response to elective ischemia employed in cardiac surgical procedures. Plasma norepinephrine concentrations increase within minutes and can remain elevated for periods of up to 20 h (419) depending on the severity of the ischemic insult and ensuing stress response. This elevates circulating plasma FFA concentrations by promoting adipose tissue lipolysis (315) and suppresses pancreatic insulin secretion and peripheral insulin sensitivity (94, 338, 520). Furthermore, elevated plasma concentrations of hydrocortisone accompany the stress of ischemia, having permissive effects on adipose tissue lipolysis and blunting insulin sensitivity (518). An increase in circulating plasma FFAs during and after ischemia thus increases the delivery of fatty acids to the myocardium and can alter fatty acid utilization during both the ischemic and postischemic period.

B. Ischemia-Induced Alterations in Fatty Acid β -Oxidation

The primary effect of ischemia is a lack of oxygen and nutrient supply and decreased clearance of metabolic by-products from the affected region(s) of the myocardium (427). When considering the myocardial effects of fatty acids during and following ischemia, it is important to recognize that fatty acids can have differing effects depending on whether the myocardium is hypoxia or ischemic. The obligate requirement for oxygen in the process of oxidative phosphorylation results in a rapid decrease in ATP production from the catabolism of fatty acids and pyruvate in proportion to the degree of ischemia. However, fatty acid β -oxidation remains a major source of residual oxidative metabolism (166, 343, 350, 682) with no increase in the relative contribution of carbohydrate oxidation (400, 461). There is a rapid acceleration in the conversion of pyruvate to lactate via lactate dehydrogenase and the regeneration of NAD^+ from NADH in an effort to maintain anaerobic glycolysis. Although glycolysis can provide a limited amount of ATP during ischemia, the hydrolysis of glycolytically derived ATP in the absence of subsequent pyruvate oxidation leads to an accumulation of lactate and H^+ (122, 519), which can further aggravate ionic disturbances brought

about by ischemia. Thus, during ischemia, when glycolysis is accelerated, a greater proportion of ATP hydrolysis must be diverted towards performing chemical work (re-establishing ionic homeostasis). It should be noted that accumulation of lactate and H^+ is less of an issue if the cardiac myocyte is exposed to hypoxia or a very mild ischemia, as opposed to a severe ischemia, since these by-products of glycolysis are rapidly removed from the cardiac myocyte. Thus, while high levels of fatty acid can aggravate lactate and H^+ production during and after severe ischemia, there is little evidence to support a detrimental effect of high fatty acid levels in hearts exposed to hypoxia or very mild ischemia.

With total ischemia there is an accumulation of reducing equivalents in the form of NADH and FADH_2 (427). Both the acyl CoA dehydrogenase and 3-hydroxyacyl CoA dehydrogenase enzyme reactions of fatty acid β -oxidation are sensitive to the redox state of the matrix (NAD^+/NADH and FAD/FADH_2 ratios)(428). The inhibition of fatty acid β -oxidation secondary to the accumulation of reducing equivalents can result in the accumulation of fatty acid intermediates in distinct cellular compartments. Fatty acyl carnitine species can accumulate in both the mitochondrial matrix and cytosol, whereas fatty acyl CoA species accumulate primarily in the mitochondrial matrix as this pool of CoA does not exchange with the relatively small cytosolic CoA pool (255). The accumulation of these acyl carnitine and acyl CoA esters promotes disruption of mitochondrial cristae and the formation of amorphous intramitochondrial densities, changes that may ultimately disrupt mitochondrial function (267).

C. Ischemia-Induced Alterations in the Subcellular Control of Fatty Acid β -Oxidation and Fatty Acid β -Oxidation in the Postischemic Period

Alterations in the subcellular control of fatty acid β -oxidation also contribute to changes in myocardial fatty acid metabolism brought about by ischemia (654). Myocardial ischemia is accompanied by the rapid activation of AMPK, and the subsequent phosphorylation and inhibition of ACC (312, 313). These former changes coupled with the relative maintenance or increase in the activity of MCD results in a decrease in myocardial malonyl CoA content during no-flow ischemia in ex vivo rat hearts (312), but not in vivo in pigs subjected to low flow ischemia (604) or ischemia caused by simultaneous flow constriction and dobutamine infusion (608). A reduction in malonyl CoA content relieves the inhibition of CPT 1, allowing fatty acid β -oxidation to increase by virtue of the increased entry of fatty acyl CoA moieties into the mitochondrial matrix. These effects contribute to the continued contribution of fatty acid β -oxidation to residual oxidative ATP generation during myocardial ischemia (166, 682).

The activation of AMPK persists during reperfusion following ischemia and is associated with the changes in ACC and MCD activity described above, resulting therefore in a marked decrease in myocardial malonyl CoA content (312). Thus, during reperfusion, the rates of fatty acid β -oxidation recover rapidly to preischemic values at the expense of glucose oxidation, while contractile function remains depressed (401, 633). This results in a greater contribution of fatty acid β -oxidation to oxidative ATP production during reperfusion following ischemia. However, the recovery of fatty acid β -oxidation at the expense of glucose oxidation contributes to an uncoupling of glucose metabolism, where glycolysis is disproportionately greater than subsequent pyruvate oxidation, thus aggravating intracellular acidosis, and impairing the recovery of cardiac function and efficiency despite the restoration of coronary flow (348).

The marked decrease in ATP production during ischemia leads to the inhibition of the $\text{Na}^+\text{-K}^+$ -ATPase which is responsible for the extrusion of three Na^+ in exchange for 2 K^+ and is crucial in regulating resting membrane potential (42). Impaired function of the $\text{Na}^+\text{-K}^+$ -ATPase thus results in intracellular Na^+ overload. Impaired activity of the sarcoplasmic Ca^{2+} -ATPase, which is responsible for the reuptake of Ca^{2+} following myocyte contraction, contributes to Ca^{2+} overload. As Ca^{2+} is required for cardiac muscle contraction, it is a major determinant of the pathophysiology of ischemic and postischemic contractile dysfunction, via mechanisms involving decreased responsiveness of the contractile proteins to activator Ca^{2+} (49). Intracellular acidosis itself impairs the response of the contractile filaments to Ca^{2+} , thereby contributing to the impaired recovery of function during reperfusion. The increased contribution of fatty acid β -oxidation to myocardial energy requirements again at the expense of pyruvate oxidation during reperfusion, in conjunction with the alterations in ionic homeostasis occurring during ischemia, prime the myocardium for further injury. The normalization of extracellular pH during the postischemic period produces a large pH gradient across the sarcolemmal membrane promoting $\text{Na}^+\text{-H}^+$ exchange, and further aggravating intracellular Na^+ overload. This in turn promotes reverse mode $\text{Na}^+\text{-Ca}^{2+}$ exchange (31), and the sequelae of events associated with intracellular Ca^{2+} overload, including contracture, mitochondrial dysfunction, the activation of Ca^{2+} -dependent proteases, and cardiac myocyte cell death culminating in the impaired recovery of cardiac function and efficiency.

VI. TARGETING FATTY ACID METABOLISM AS A THERAPEUTIC INTERVENTION FOR HEART DISEASE

The modulation of myocardial energy substrate metabolism, particularly shifting energy substrate preference

from the use of fatty acids towards the use of glucose as an oxidative fuel, is a novel therapeutic intervention to enhance the preservation of mechanical function and efficiency in various forms of ischemic heart disease and heart failure. Pharmacological agents that inhibit fatty acid β -oxidation and favor the use of glucose as an oxidative fuel have recently received considerable attention (97, 137, 139, 265, 320, 333, 357, 403, 602, 609, 647, 652, 702). Altering the balance between fatty acid and glucose use can be elicited through the use of pharmacological agents that act at a variety of levels on the pathways of fatty acid and glucose metabolism and, as such, alter the balance and contribution of these pathways to cardiac energetics and function by increasing the efficiency of both ATP generation and utilization. With regard to fatty acid metabolism, such effects can be obtained by altering the availability of circulating substrates, mitochondrial uptake of fatty-acyl CoAs, as well as through altering the process of fatty acid β -oxidation, either directly or indirectly via the stimulation of pyruvate oxidation (see Fig. 7).

A. Therapies Targeting the Availability of Circulating Energy Substrates

1. Glucose-insulin-potassium

The beneficial effects of glucose-insulin-potassium (GIK) on myocardial energy substrate metabolism that underlie cardioprotection were originally proposed as a stimulation of glucose disposal via glycolysis and a reduction in circulating FFA concentrations with a resultant decrease in myocardial fatty acid β -oxidation (453, 597). Experimental studies utilizing models of myocardial infarction have indeed demonstrated that infusion of GIK solutions can maintain circulating plasma glucose concentrations, while suppressing circulating FFA concentrations (271). These alterations in the concentrations of circulating substrates induce a shift in myocardial metabolism from the utilization of fatty acids to the utilization of glucose as an energy substrate, effects that decrease the release of both lactate dehydrogenase and creatine kinase, as well as decreasing infarct size and improving the recovery of postischemic cardiac function (271, 719). Interestingly, these cardioprotective effects are not definitive as experimental studies also demonstrate a lack of infarct size reduction in response to GIK treatment (300). This may be related to the complex effects of GIK on myocardial energy metabolism, specifically its ability to disproportionately stimulate glycolysis to a greater extent than glucose oxidation (i.e., pyruvate oxidation) and, hence, accelerate the rate of myocardial H^+ production from uncoupled glucose metabolism (164).

Increased glucose load itself results in hyperglycemia, which may attenuate or obscure the protective ef-

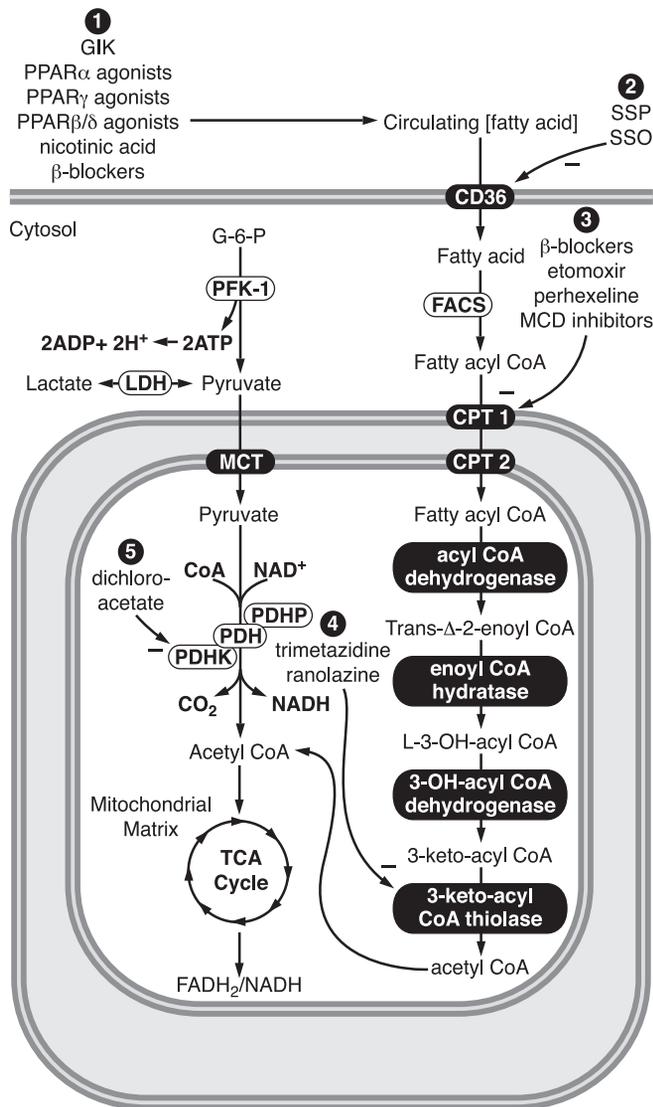


FIG. 7. Targeting fatty acid metabolism as a treatment for ischemic heart disease. Fatty acid metabolism can be targeted at numerous levels for the treatment of ischemic heart disease. Specifically, there are a number of compounds that decrease the circulating availability of fatty acids (1), protein-mediated uptake of fatty acids (2), mitochondrial uptake of fatty acids (3), and fatty acid β -oxidation directly (4) and indirectly (5). Specifics pertaining to each compound are described in the text.

ffects of administered insulin. Hyperglycemia can contribute to augmented ischemic damage by increasing cardiac myocyte apoptosis (384, 582, 614) and oxidative stress (411, 412). Furthermore, hyperglycemia exerts proinflammatory (385) and prothrombotic effects including platelet hyperreactivity and elevated plasminogen activator inhibitor-1 (a negative regulator of fibrinolysis) levels (463), in addition to impairing microcirculatory function (258). Taken together, these unwanted effects of hyperglycemia may be especially harmful in the clinical setting of acute myocardial infarction and outweigh the favorable effects of reducing circulating FFA concentrations. Therefore,

the differences in clinical outcomes with GIK may thus be impacted upon by the differing doses employed, the timing of GIK administration, the patient population studied, as well as the possible detrimental effects of hyperglycemia. However, there are important differential effects with regard to increasing glucose uptake versus glucose oxidation. As we discussed in section 11K, the proportion of glycolytic pyruvate being oxidized, and the subsequent intracellular acidosis that follows, may actually be more important with regard to functional outcome, rather than simply increasing glycolytic ATP production. Thus further studies investigating the ability of GIK to alter myocardial fatty acid β -oxidation rates to limit and/or ameliorate ischemic injury are needed.

The above effects of targeting myocardial energy metabolism with GIK are also transferred to the clinical setting, where there remains a lack of a clear consensus regarding the beneficial, neutral, and/or deleterious effects of GIK in myocardial ischemia. Meta-analysis of GIK treatment in the prethrombotic era demonstrate its ability to reduce mortality associated with myocardial infarction (153), as do clinical trials carried out in the thrombolytic era including the Diabetic Patients with Acute Myocardial Infarction (DIGAMI) study (382), the Estudios Cardiológicos Latinoamerica (ECLA) Collaborative Group study (128), and the Dutch Glucose-Insulin-Potassium Study 1 (GIPS 1). However, the Polish (Pol) GIK trial did not demonstrate any reduction in cardiovascular mortality with GIK (658), whereas the Dutch GIPS 2 study had to be stopped early due to a potentially higher mortality in the GIK group (639). Recently, the combined analysis of the use of GIK in the Organization for the Assessment of Strategies for Ischemic Syndromes-6 (OASIS-6) and ECLA trials for S-T segment elevation myocardial infarction (STEMI) failed to demonstrate any reduction in mortality, while actually demonstrating increased mortality following early (within 2–4 h of symptom onset) treatment, likely owing to increased glucose, potassium, and fluid load (127). The differences in clinical outcomes with GIK may thus be impacted upon by the differing doses employed, the timing of GIK administration, as well as the patient population studied. Thus further studies investigating the ability of GIK to alter myocardial fatty acid β -oxidation to limit and/or ameliorate ischemic injury are needed.

2. PPAR ligands

PPARs are members of the ligand-activated nuclear hormone receptor superfamily and exert major influences on lipid metabolism specifically by regulating the balance between fatty acid β -oxidation and fatty acid storage through regulating the expression of enzymes involved in fatty acid β -oxidation and lipogenesis (596). Three distinct PPAR isoforms (PPAR α , PPAR γ , PPAR β/δ) have

been identified in mammals with differing tissue distributions.

A) PPAR α LIGANDS. PPAR α is predominantly expressed in tissues with a high capacity for fatty acid β -oxidation, including heart, skeletal muscle, and liver (189, 596), and represents the molecular target of antihyperlipidemic fibrates such as gemfibrozil, clofibrate, and fenofibrate. Fibrates can increase the expression and activity of extracardiac FACS (561), an effect that may contribute to the ability of these drugs to increase the fatty acid binding capacity of cytosolic proteins in liver and kidney (474). Interestingly, fibrates decrease the fatty acid binding capacity of cardiac cytosolic proteins (474). Furthermore, these drugs also increase the hepatic expression of enzymes of fatty acid β -oxidation (108). In combination, these effects increase extracardiac fatty acid β -oxidation and decrease circulating FFA concentrations, thereby decreasing the level of FFA to which the heart is exposed, ultimately decreasing myocardial fatty acid β -oxidation. Experimental studies have demonstrated the cardioprotective effects of fibrates, specifically a reduction in infarct size (678), and an improved recovery of postischemic cardiac function (486). Interestingly, a recent report demonstrates that PPAR α agonist (GW7467)-mediated cardioprotection in vivo is associated with an increase in fatty acid β -oxidation following coronary artery occlusion and subsequent reperfusion, despite a marked reduction in circulating FFA concentrations in the postischemic period (715). Furthermore, the cardioprotective effects of GW7467 were abolished in PPAR α -null mice. The observed increase in fatty acid β -oxidation may have been manifest as a result of the improved recovery of postischemic function, and thus greater cardiac energy demand, while the loss of GW7467-mediated cardioprotection in PPAR α -null mice may be attributed to an inability of the PPAR α agonist to increase extracardiac fatty acid utilization, and thereby limit the concentration of circulating FFA to which the myocardium is exposed.

B) PPAR γ LIGANDS. PPAR γ is predominantly expressed in adipose tissue, and only low levels are detectable in both skeletal and cardiac muscle. It also represents the molecular target of the antidiabetic thiazolidinedione drugs (i.e., pioglitazone, troglitazone, rosiglitazone). Thiazolidinediones prevent the ectopic deposition of lipid in nonadipose tissues not suited for excess lipid storage and, as such, can promote adiposity by increasing the sequestration of lipids in adipose tissue itself. Experimental studies indicate that thiazolidinediones decrease circulating plasma TAG (714) and FFA concentrations (714, 726) while promoting myocardial glucose and lactate uptake, and glucose oxidation (590, 714, 726). These alterations in myocardial energy substrate availability and metabolism improve the recovery of postischemic cardiac function (714, 716, 726).

Despite the ability of thiazolidinediones to induce the potentially beneficial shifts in myocardial energy sub-

strate metabolism described above, their use in clinical scenarios where inducing such a shift in energy metabolism may be desirable is not without concern. Importantly, thiazolidinediones have the undesirable effect of increasing fluid retention and aggravating peripheral edema in diabetic heart failure patients due to their vasodilatory effects (344). Recent meta-analyses also demonstrate that the use of thiazolidinediones increases the risk of myocardial infarction and death from cardiovascular causes in type 2 diabetes mellitus patients (344, 436). The mechanisms underlying the increased risk of myocardial infarction associated with the use of thiazolidinediones remain unresolved, however, may be related to adverse alterations in circulating lipoprotein profile, specifically an increase in low-density lipoprotein (LDL) concentration as well as increase in intravascular volume which has the potential to elicit myocardial ischemia by increasing oxygen demand in susceptible individuals (436). Furthermore, PPAR γ agonists can decrease the expression of vascular endothelial growth factor (VEGF) receptor 1 and VEGF 2 expression and endothelial tube formation in vitro, as well as inhibiting VEGF-induced angiogenesis in vivo (rat cornea) (699). Whether these effects are transferable to the coronary circulation is not known; nonetheless, these effects do have the potential to decrease the formation of collateral vessels in the setting of ischemia heart disease and may therefore contribute to the increased risk of myocardial infarction. Thus the use of thiazolidinediones to alter myocardial energy substrate metabolism in any cardiovascular disease state warrants further study and assessment of safety.

C) PPAR β/δ LIGANDS. PPAR β/δ is the predominant PPAR isoform expressed in skeletal muscle, as well as white and brown (in rodents) adipose tissue (377); however, it is not as well characterized as either PPAR α or PPAR γ . Nonetheless, experimental studies implicate PPAR β/δ in the regulation of both skeletal muscle and adipose tissue fatty acid metabolism. The activation of PPAR β/δ increases skeletal muscle and adipose tissue fatty acid β -oxidation (632, 674), and by increasing extracardiac fatty acid metabolism, may decrease the plasma fatty acid concentrations to which the heart is exposed and confer cardioprotection following ischemia.

3. Nicotinic acid

Nicotinic acid is a broad-spectrum antiatherogenic compound that decreases circulating VLDL and LDL levels, while increasing high-density lipoprotein (HDL) levels. The beneficial effects of nicotinic acid in the treatment of ischemic heart disease are primarily attributed to its antiatherogenic properties including decreased atherosclerotic lesion progression and increased lesion regression (71, 398). However, nicotinic acid can also alter energy metabolism. Following dosing, nicotinic acid is

uniquely distributed to adipose tissue, likely owing to the expression of a specific high-affinity G protein-coupled receptor (641). Nicotinic acid inhibits adipose tissue lipolysis and thus decreases circulating FFA concentrations to ultimately decrease myocardial fatty acid β -oxidation. In human studies, nicotinic acid increases the cardiac respiratory quotient, in the absence of alterations in the oxygen extraction ratio, effects consistent with a shift in myocardial energy substrate metabolism from fatty acid β -oxidation towards carbohydrate oxidation (72, 328). These effects on myocardial energy substrate metabolism likely contribute to the anti-ischemic effects of nicotinic acid.

4. β -Adrenoceptor antagonists

β -Adrenoceptor antagonists are proposed to exert their anti-ischemic effects via oxygen sparing attributed to both negative inotropic and negative chronotropic effects. Presumably, by reducing neuro hormonal activation, β -adrenoceptor antagonists could reduce catecholamine-induced lipolysis and therefore decrease circulating plasma FFA concentrations. β -Adrenoceptor antagonists decrease the mobilization of FFA from adipose tissue (154) and can lower plasma FFA concentrations (58, 433). Furthermore, increased sympathetic activity, reflected by increased circulating concentrations of catecholamines and FFAs, is reduced by the β -adrenoceptor antagonist propranolol during the course of myocardial infarction (419). These effects may decrease the availability of circulating FFAs for myocardial fatty acid β -oxidation. Indeed, two small clinical studies suggest β -adrenoceptor antagonists can decrease fatty acid uptake and oxidation (256, 671), while increasing LV function in the absence of increased oxygen utilization (147, 148). These changes are consistent with increased myocardial carbohydrate metabolism and increased cardiac efficiency.

B. Therapies Targeting Sarcolemmal Fatty Acid Uptake

Sulfo-*N*-succinimidyl esters of long-chain fatty acids including sulfo-*N*-succinimidyl-palmitate (SSP) and sulfo-*N*-succinimidyl-oleate (SSO) are described as inhibitors of FAT/CD36 and can inhibit CPT 1 (65) and, hence, protein-mediated sarcolemmal and mitochondrial fatty acid uptake (111). Studies carried out in cardiac myocytes and cardiac giant membrane vesicle preparations demonstrate that these compounds can decrease long-chain fatty acid uptake (374, 375). Furthermore, the compound SSP decreases palmitate uptake in isolated rat hearts (631). Although functional studies using these inhibitors in experimental models of myocardial ischemia-reperfusion are lacking, inhibition of CD36 via genetic ablation results in a compensatory increase in myocardial glucose

oxidation during postischemic reperfusion (311), attenuates age-related increases in intramyocardial TAG, while improving mitochondrial ATP production and enhancing cardiac function (303). Taken together, these findings may suggest that inhibiting myocardial fatty acid uptake may be a viable approach to treat various cardiac pathophysiological states.

C. Therapies Targeting Mitochondrial Fatty Acid Uptake

CPT 1 is a rate-controlling enzyme mediating the mitochondrial uptake of fatty acids. Therefore, pharmacological agents that inhibit CPT 1 can elicit anti-ischemic effects via the modulation of myocardial fatty acid metabolism. Several CPT 1 inhibitors have been developed for this purpose and include the compounds perhexiline, etomoxir, and oxfenecine. Several experimental studies demonstrate that the anti-ischemic effects of these compounds are attributed to an increase in myocardial glucose oxidation, elicited at the expense of fatty acid β -oxidation (266, 287, 366, 369, 408, 652). Of these CPT 1 inhibitors, perhexiline has received the most attention.

1. Etomoxir

Etomoxir {2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate} is an irreversible inhibitor of CPT that was originally designed as an antidiabetic agent (500), which can also alter the balance between myocardial fatty acid β -oxidation and glucose oxidation, such that glucose oxidation is favored. In experimental models of ischemia and reperfusion, etomoxir improves the recovery of ventricular function following ischemia (364, 366, 369). This cardioprotective effect is also afforded to the postischemic diabetic heart (559, 669) and may suggest the possible clinical utility of etomoxir in patients with diabetic cardiomyopathy. The protective effects of etomoxir in the postischemic period are accompanied by increased rates of myocardial glucose oxidation and an increased production and utilization of ATP for contractile work due to the stimulation of the cardiac pyruvate dehydrogenase complex (via the Randle cycle) (59, 364, 366, 369).

Although clinical experience with etomoxir is very limited, its potential beneficial effects on heart function have been assessed in a small (15 patients) uncontrolled, open-label study of patients with NYHA class II heart failure (558). Following 3 mo of etomoxir treatment (80 mg), there was an improvement in LV ejection fraction, cardiac output at peak exercise, and clinical status (558); however, this trial was not able to assess the long-term safety of etomoxir treatment. The more recent, etomoxir for the recovery of glucose oxidation (ERGO) study had to be stopped early as several patients with NYHA class II-class III heart failure in the treatment group were found

to have elevated liver transaminase enzyme levels (240). This adverse effect may be related to the irreversible inhibition of CPT 1 in response to etomoxir, an effect that may allow toxicity to manifest from its excessive accumulation. This study did not detect any significant improvement in the etomoxir group (40 and 80 mg) compared with placebo (likely due to limited power); however, there was a trend to increased exercise time.

2. Perhexeline

Perhexeline was frequently prescribed as an anti-ischemic agent for the treatment of angina in the 1970s; however, its use declined in the 1980s due to adverse effects including hepatic toxicity (steatosis and necrosis) and peripheral neuropathy (334), attributed to the accumulation of phospholipids likely occurring secondary to the inhibition of CPT 1 (23). Of importance is the fact that the hepatic toxicity of perhexeline is due to the inhibition of the hepatic isoform of CPT 1 (125). *In vitro* studies clearly demonstrate that the cardiac isoform of CPT 1 is more sensitive to inhibition by perhexeline (288), an effect that allows for the use of dose titration to avoid or limit adverse effects. Maintaining plasma perhexeline concentration within the therapeutic range of 150–600 $\mu\text{g/l}$ preserves its anti-ischemic effects, while minimizing its adverse effects (104). Several clinical trials have demonstrated the beneficial effects of perhexeline in aortic stenosis, heart failure, and angina pectoris (104, 333, 650). Thus the inhibition of CPT 1 and the resultant decrease of fatty acid β -oxidation is an effective therapeutic strategy that can be exploited in various manifestations of ischemic heart disease.

3. Malonyl CoA decarboxylase inhibitors

Selective MCD inhibitors using human recombinant MBP fusion MCD protein have been screened and optimized to inhibit MCD from both rat and swine heart to similar extents (137). These compounds are effective at increasing myocardial malonyl CoA content and stimulating myocardial glucose oxidation secondary to an inhibition of CPT 1 (137, 513, 608). The MCD inhibitor CBM-301106 elevates myocardial malonyl CoA content during demand-induced ischemia in the swine heart, an effect associated with reduced fatty acid β -oxidation, increased glucose oxidation, and a decrease in lactate release (608). The ability of MCD inhibitors (CBM-300864) to elicit the aforementioned effects is also preserved in experimental models of severe, global ischemia-reperfusion, where these compounds stimulate glucose oxidation and enhance the recovery of LV function during the postischemic period (137). The cardioprotective effects of MCD inhibition following ischemia have furthermore been corroborated via the generation of MCD-deficient mice, suggesting that the inhibition of malonyl CoA may be a

therapeutically relevant option in the treatment of ischemic heart disease (139).

D. Therapies Partially Inhibiting Mitochondrial Fatty Acid β -Oxidation

1. Trimetazidine

3-KAT, the terminal enzyme of fatty acid β -oxidation, is recognized as a therapeutic target in the treatment of ischemic heart disease. Trimetazidine is a partial fatty acid β -oxidation inhibitor that competitively inhibits long-chain 3-KAT (281, 357), as demonstrated by the ability of increasing concentrations of the 3-KAT substrate 3-ketohexadecanoyl-CoA to surmount inhibition (357). Trimetazidine is clinically utilized as an antianginal therapy throughout Europe and in over 90 countries (467). By inhibiting fatty acid β -oxidation, trimetazidine causes a reciprocal increase in glucose oxidation (281, 357), thereby decreasing the production of H^+ arising from glycolysis uncoupled from glucose oxidation. Interestingly, in the setting of pressure-overload cardiac hypertrophy, where the rates of fatty acid β -oxidation are depressed, trimetazidine confers cardioprotection independently of alterations in fatty acid β -oxidation (542). Rather, trimetazidine attenuates the elevated rates of glycolysis and increases glucose oxidation to limit the production of H^+ attributed to glucose metabolism. The inhibition of glycolysis coupled with the increase in glucose oxidation, or the partial inhibition of fatty acid β -oxidation and the parallel stimulation of glucose oxidation, can limit ischemia-induced disturbances in myocardial ionic homeostasis. Specifically, the improved coupling of glucose metabolism attenuates intracellular acidosis as well as Na^+ and Ca^{2+} overload (510) during ischemia and subsequent reperfusion (98, 510) and improves the recovery of postischemic cardiac function (413). Trimetazidine also exerts favorable effects on cardiac myocyte Ca^{2+} handling that can limit ischemic myocardial injury, including reductions in Ca^{2+} current (297), prevention of elevated $[\text{Ca}^{2+}]_i$, and preservation of SR Ca^{2+} -ATPase activity (402) that may limit or prevent cytosolic Ca^{2+} overload. Therefore, the metabolic effects of trimetazidine are permissive to increasing cardiac efficiency by sparing ATP hydrolysis from being utilized to correct ionic homeostasis, and making it available to fuel contractile work.

The effects of trimetazidine in experimental studies can be extrapolated to the clinical setting, where the drug is efficacious in the treatment of angina, myocardial infarction, and heart failure (265). The anti-ischemic effects of trimetazidine in the treatment of angina include an increased time to 1-mm S-T segment depression and decreased weekly nitrate consumption (97). In the setting of acute myocardial infarction, the cardioprotective effects

of trimetazidine are evident as a reduction in reperfusion arrhythmias and a more rapid resolution of S-T segment elevation (465, 610). The addition of trimetazidine to treatment regimens also improves NYHA functional class, LV end-diastolic volume, and ejection fraction in individuals with heart failure and ischemic cardiomyopathy (170, 171), as well as idiopathic dilated cardiomyopathy (647). Thus the partial inhibition of fatty acid β -oxidation, via the reversible, competitive inhibition of 3-KAT, at least in part, attenuates several consequences of various forms of ischemic heart disease.

2. Ranolazine

Ranolazine is an antiangina drug approved in the United States for the treatment of chronic stable angina (567). It has been shown to suppress fatty acid β -oxidation in rat cardiac and skeletal muscle and result in a reciprocal increase in glucose oxidation (388, 389), which has been associated with indirect activation of PDH (100, 101). While there is no direct evidence for this mechanism in patients, subgroup analysis of a placebo-controlled clinical trial with ranolazine showed a significant reduction in glycosylated hemoglobin A1c that was similar to that observed with approved antidiabetic drugs (77), consistent with accelerated systemic glucose clearance secondary to effects on muscle metabolism. In experimental studies, ranolazine preserves mitochondrial structure, decreases tissue Ca^{2+} content, and decreases postischemic ventricular fibrillation (200, 201). Ranolazine also attenuates myocardial stunning and reduces infarct size (211, 212). These effects may be explained by a shift in myocardial energy metabolism from fatty acid β -oxidation towards glucose oxidation, which can increase ATP generation at any given level of oxygen consumption, and/or a sparing of ATP from correcting ionic homeostasis and thus driving contractile function (100, 101, 389). In a canine model of heart failure, acute treatment with ranolazine increases cardiac ejection fraction, stroke volume, and mechanical efficiency in the absence of increased oxygen consumption (81, 535), and 3 mo of treatment prevents progressive LV remodeling and contractile dysfunction (499). Interestingly, ranolazine-induced cardioprotection has also been demonstrated to be dissociated from alterations in fatty acid β -oxidation (672), thereby suggesting additional/alternative mechanisms for ranolazine-induced cardioprotection. Recent reports implicate the ability of ranolazine to directly inhibit the late Na^+ current and prevent adverse increases diastolic $[\text{Ca}]_i$ via Na^+ -dependent Ca^{2+} overload in limiting ischemic myocardial injury (174, 600).

In the clinical setting, ranolazine is an effective anti-ischemic agent in the treatment of angina pectoris, where, when utilized as monotherapy, or added to standard antianginal regimens, it increases time to 1-mm S-T segment

depression and reduces the number of weekly angina attacks, and hence weekly nitroglycerin consumption (78, 79, 528, 612). These effects of ranolazine also extend to diabetic patients (640). Clinical trials also demonstrate the ability of ranolazine to decrease the incidence of ventricular tachycardia, supraventricular tachycardia, and ventricular pauses (418, 568). These antiarrhythmic effects likely arise from the ability of ranolazine to inhibit the late Na^+ current (36). The anti-ischemic and antiarrhythmic effects of ranolazine are not mutually exclusive, as they occur at similar concentrations.

E. Therapies Overcoming Fatty Acid-Induced Inhibition of Glucose Oxidation

1. Dichloroacetate

Dichloroacetate also promotes myocardial glucose oxidation at the expense of myocardial fatty acid β -oxidation; however, unlike trimetazidine and ranolazine, dichloroacetate stimulates the mitochondrial pyruvate dehydrogenase complex by directly inhibiting the activity of pyruvate dehydrogenase kinase. Experimental studies have demonstrated the ability of dichloroacetate to enhance the postischemic recovery of cardiac function in vitro as well as in vivo (257, 401, 604). An increase in cardiac efficiency, and an improved coupling between glycolysis and glucose oxidation, accompany the cardioprotective effects of dichloroacetate (347, 348). Clinical experience with dichloroacetate is limited; however, in a small clinical trial, dichloroacetate increased LV stroke volume and myocardial efficiency, effects accompanied by increased lactate utilization (675). As the metabolic effects of dichloroacetate are similar to trimetazidine and ranolazine, it may be relevant in the therapeutic management of angina pectoris; however, its anti-ischemic efficacy has yet to be assessed in such a setting.

VII. SUMMARY

Cardiac fatty acid β -oxidation is a dynamic process that can quickly increase or decrease to adapt to alterations in cardiac energy demand or changing environment. Although there exists a lot of controversy with regard to fatty acid β -oxidation rates and the accumulation of intramyocardial lipid, recent evidence has implicated high cardiac fatty acid β -oxidation rates in obesity or diabetes as being an important contributor to the development of cardiomyopathies. Alterations in fatty acid β -oxidation also have important implications on cardiac function in both heart failure and ischemic heart disease. Of importance is that emerging evidence suggests that inhibition of fatty acid β -oxidation may be a useful approach to improve heart function in the setting of obesity,

diabetes, heart failure, and ischemic heart disease. Future animal studies should look to combine these various disease models (i.e., DIO and heart failure), as opposed to studying them in isolation, due to the fact that our obese, diabetic, and cardiovascular disease patient populations often encompass the same individuals.

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