Cardiac Energy Metabolism in Heart Failure Associated with Obesity and Diabetes

Gary D. Lopaschuk

Abstract Obesity and diabetes are important risk factors for the development of heart failure. The metabolic abnormalities that accompany obesity and diabetes result in dramatic alterations in cardiac energy metabolism, which can contribute to the progression of heart failure. Elevated rates of fatty acid oxidation and depressed rates of glucose oxidation characterize the cardiac metabolic profile in the setting of obesity-induced insulin resistance and diabetes. This metabolic profile results in a marked cardiac insulin resistance, which is accompanied by decrements in both cardiac function and efficiency, and by the accumulation of potentially toxic fatty acid metabolites in the heart. Acetylation of various mitochondrial and glycolytic enzymes are altered in obesity and diabetes, which may also contribute to the pathogenesis of heart failure in obesity and diabetes. As a result, therapeutic interventions that prevent or reverse the energy metabolic switch in the heart of obese and diabetic individuals, and/or the accumulation of fatty acid metabolites may lessen the severity of heart failure. These interventions include inhibiting myocardial fatty acid oxidation, stimulating glucose oxidation, restoring myocardial insulin sensitivity, preventing myocardial fatty acid metabolite accumulation, and inhibiting the acetylation of key enzymes involved in fatty acid oxidation. This paper reviews the metabolic alterations that occur in heart failure associated with obesity and diabetes, and the molecular mechanisms responsible for these changes.

Keywords Fatty acid oxidation • Glucose oxidation • Lysine acetylation • Cardiac insulin-resistance • Lipotoxicity

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1 Introduction

Obesity and diabetes are major health concerns in our population, with the incidence rapidly rising in both Canada and the world. Among the many complications associated with obesity and diabetes is an increased risk of developing heart failure, a complex clinical syndrome [1, 2], characterized by the progressive inability of the heart to fill with, and eject, adequate amounts of blood to meet the needs of the body. This increased risk of developing heart failure in obese and diabetic individuals persists even after adjusting for independent factors including coronary artery disease and hypertension [3–5]. As a result, a considerable research effort has focused on the mechanisms responsible for the increased prevalence of heart failure in obesity and diabetes. Potential contributing factors identified thus far include: (1) increased oxidative stress [6], (2) development of cardiac autonomic neuropathies [7], (3) accelerated apoptosis [8, 9], (4) accelerated inflammatory responses [9–11], (5) accelerated fibrosis [12], (6) altered cardiac Ca^{2+} and Na^{+} handling [13], (7) production of advanced glycation end products (AGE) and receptors for AGEs activation [14], (8) increased polyol pathway activity [15], (9) activation of NADPH oxidase [16, 17], (10) increased O-linked β-N-acetylglucosamine [18], and (11) alterations in cardiac energetics (discussed below).

Heart failure in obesity and diabetes is characterized by the early development of left ventricular (LV) diastolic dysfunction [19], increased LV mass, increased LV wall thickness, and the eventual development of LV systolic dysfunction [20]. This is accompanied by changes in control of fatty acid metabolism at both the level of the heart and skeletal muscle [22–28]. As heart failure progresses, myocardial ATP and PCr content decreases [23–28], with a decrease in the PCr/ATP ratio correlating with NYHA functional class 2 [29, 30]. Defects in the rates of oxygen consumption and mitochondrial electron transport chain activity (which impact oxidative phosphorylation, and hence ATP generation) also accompany heart failure (see for review [31]). Heart failure also impairs insulin signaling [32, 33]. These deficits in insulin sensitivity and energy generation contribute to the pathogenesis and progression of heart failure in obesity and diabetes. Evidence is emerging that the exacerbation of heart failure in obesity and diabetes is due, in part, to the alterations in the use of fatty acids as a source of ATP production.

2 Cardiac Fatty Acid Use in Obesity, Diabetes, and Heart Failure

While fatty acids are a major energy source of the heart, fatty acid uptake and subsequent mitochondrial fatty acid oxidation must be coordinately regulated in order to ensure adequate, but not excessive supply, for cardiac energetic requirements (Fig. 1). The presence of diabetes and/or obesity induced insulin-resistance can markedly alter this regulation, leading to adverse consequences on cardiac

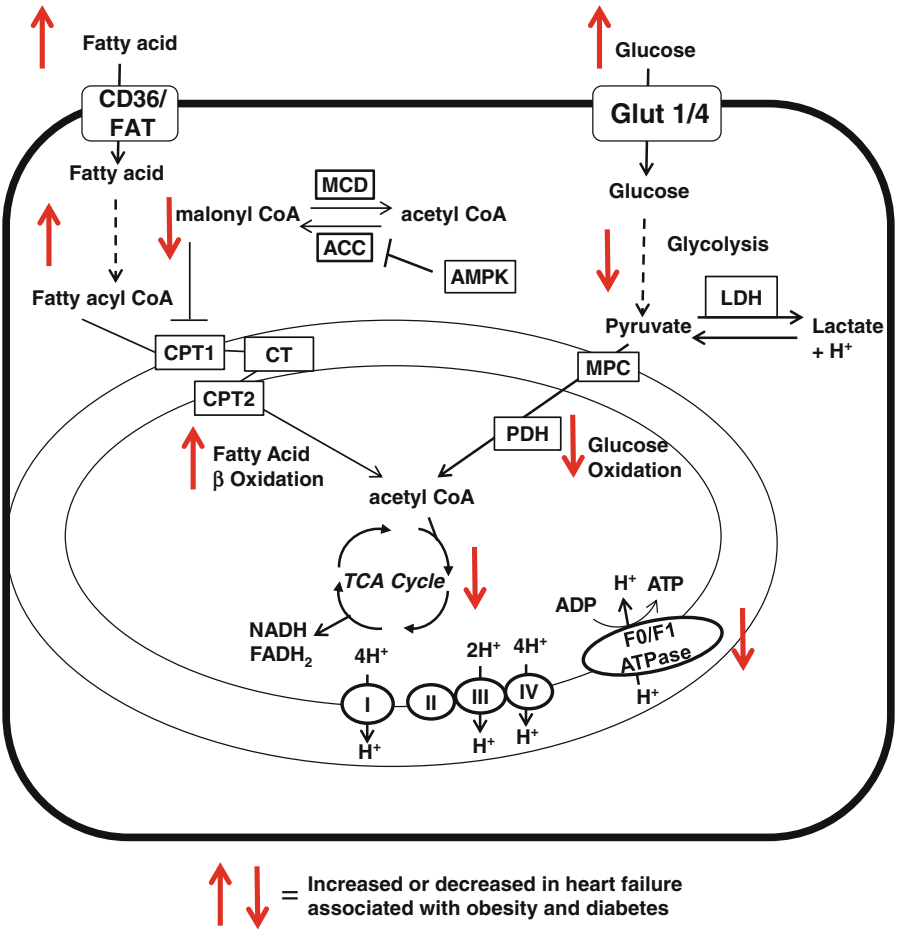

Fig. 1 Alterations in cardiac energy metabolism that occur during heart failure associated with obesity and diabetes

function. In particular, numerous clinical and experimental studies have shown that the heart switches to a greater reliance on fatty acid oxidation as a source of energy in obesity and diabetes. We and others have shown that fatty acid oxidation rates in the heart are increased in diabetic rats, as well as in rats and mice subjected to diet-induced obesity and in insulin-resistant *db*/*db* and *ob*/*ob* mice, with the increase in fatty acid oxidation occurring primarily at the expense of glucose oxidation [33–48]. Human studies using positron emission tomography and ^{11}C-palmitate imaging found that obese women and type 2 diabetics also have increased cardiac fatty acid oxidation [49, 50].

Heart failure itself results in significant alterations in cardiac energy metabolism, with the metabolic phenotype dependent on the stage/severity of the syndrome.

Fatty acid oxidation rates are normal in acute heart failure secondary to aortic banding in rats [51], in the failing canine heart [52], and in patients with asymptomatic hypertrophic cardiomyopathy [53]. However, in NYHA functional class III patients fatty acid use is increased [54], and is accompanied by elevated plasma lactate levels, indicative of fatty acid impairment of carbohydrate oxidation [54]. In clinically stable NYHA functional class II and III patients, cardiac fatty acid uptake [55, 56] and subsequent oxidation [55] is greater than that observed in healthy controls, while glucose uptake [56] and oxidation are lower [55]. Mitochondrial TCA cycle and oxidative phosphorylation are also depressed in heart failure [57]. In mice subjected to an abdominal aortic constriction (AAC), we show that the development of hypertrophy and diastolic heart failure is accompanied by early decreases in overall mitochondrial oxidative capacity [58]. An early change that occurs in heart failure is a decrease in overall mitochondrial oxidative metabolism, with a prominent decrease in carbohydrate oxidation [59–62]. Of importance is that a decrease in carbohydrate oxidation is primarily responsible for the decrease in mitochondrial oxidation, and fatty acid oxidation is only marginally decreased. In addition, a marked decrease in insulin sensitivity occurs in the heart during the development of diastolic heart failure [59–62]. We also recently showed that development of systolic heart failure secondary to pressure overload is accelerated in obese mice [62]. Of interest, is that decreasing obesity by switching mice to a low fat diet or by caloric restriction markedly increases insulin-sensitivity, decreases fatty acid oxidation, and improves glucose oxidation [62, 63]. We therefore propose that worsening of heart failure occurs secondary to obesity-induced changes in fatty acid oxidation, and an exacerbation of the insulin resistance that occurs in heart failure.

3 The Controversy of Fatty Acid Metabolism and Insulin-Resistance

High circulating levels of fatty acids, as well as increased uptake and esterification of fatty acids contributes to muscle insulin-resistance and cardiac lipotoxicity (see [64] for review). Decreasing muscle fatty acid uptake and/or esterification can decrease the accumulation of these toxic lipid intermediates [21, 22, 65–69]. However, a controversial strategy for decreasing lipid accumulation is based on enhancing fatty acid oxidation, which has been proposed to help remove cytoplasmic lipid metabolites, thereby improving insulin sensitivity [21, 22, 69, 70]. This concept is based on the observation that the size and number of mitochondria, as well as the activity of proteins in the respiratory chain are reduced in obese insulin-resistant humans, rodents [71–76], or subjects with type II diabetes [77–79]. However, contrary evidence suggests that several markers of mitochondrial function and fatty acid oxidative capacity (oxidative enzyme activity and protein expression) are elevated in muscle of high fat-fed mice and rats, obese Zucker rats (*fa/fa*), and *db/db* mice [80, 81], and direct measurements of fatty acid oxidation in the heart have shown that in insulin resistance fatty acid oxidation rates are accelerated

[39, 42, 82]. Furthermore, we and others have shown that inhibiting fatty acid oxidation in heart and skeletal muscle can increase insulin sensitivity [40, 41, 83, 84]. Products of incomplete fatty acid oxidation can also contribute to muscle insulin-resistance [41]. As a result, debate still exists as to whether stimulating or inhibiting muscle fatty acid oxidation is an approach to lessen insulin resistance, prevent lipid accumulation and improve contractile dysfunction.

4 High Fatty Acid Oxidation Decreases Cardiac Efficiency and Contractile Function in Obesity, Diabetes and Heart Failure

Cardiac efficiency (the amount of work performed by the heart per oxygen consumed) [85], is influenced by alterations in fatty acid oxidation [86]. This has potentially important consequences in heart failure, as well as in the setting of obesity and diabetes where rates of fatty acid use are markedly altered. As the majority of ATP utilized to drive cardiac contraction is generated by mitochondrial oxidative phosphorylation, cardiac efficiency itself can be influenced by both the efficiency of ATP generation and hydrolysis (i.e. the efficiency of converting chemical energy into mechanical energy). Interestingly, there are relatively few studies that have examined cardiac mechanical efficiency in heart failure, and there appears to be discrepant results between these studies. Studies have shown a preservation of cardiac efficiency secondary to decreases in MVO_2 [87, 88]; while, in contrast, others have demonstrated decreased cardiac efficiency secondary to oxygen wasting effects in the failing heart [89, 90]. The effects of obesity and/or diabetes on cardiac efficiency are less ambiguous. In murine models of obesity, insulin resistance, and diabetes (including leptin-deficient *ob*/*ob* and leptin receptor-deficient *db*/*db* mice) cardiac fatty acid use is increased, while cardiac efficiency is decreased [39, 42, 91–94]. The decrease occurs in response to increased MVO_2 [38, 39, 91], decreased LV work [39, 92] or a combination of both [39, 92].

5 Mechanism by Which Fatty Acid Oxidation is Altered in Obesity, Diabetes, and Heart Failure

5.1 Alterations in Fatty Acid Supply

Both human and animal studies have shown that a prevalent metabolic change in obesity/insulin resistance involves an elevation in circulating fatty acids and triacylglycerol (TAG) levels [38, 95–100], resulting in an increase in cardiac fatty acid uptake and oxidation. Increased fatty acid supply to the cardiomyocyte may also be

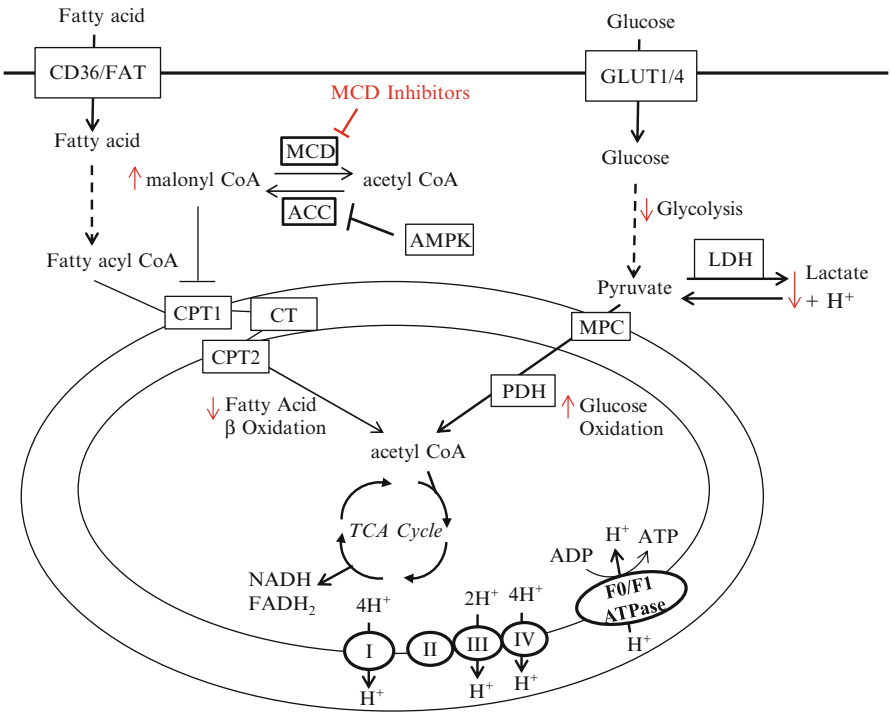

Fig. 2 Increased fatty acid uptake and oxidation in failing hearts associated with obesity and diabetes is accompanied by a marked decrease in energy production from glucose oxidation. Decreases in tricarboxylic acid (TCA) cycle activity and electron transport chain activity can lead to an increase in incomplete fatty acid oxidation. The increase in fatty acid oxidation in failing hearts associated with heart failure can be explained by: (1) an increased fatty acid supply to the heart, (2) a decrease in cardiac malonyl CoA levels resulting in a decreased inhibition of carnitine palmitoyltransferase 1 (CPT1), and/or (3) an increased acetylation of fatty acid oxidative enzymes. *FAT* fatty acid transporter, *MCD* malonyl CoA decarboxylase, *ACC* acetyl CoA carboxylase, *AMPK* AMP-activated protein kinase, *CPT* carnitine palmitoyltransferase, *CT* carnitine acylcarnitine translocase, *PDH* pyruvate dehydrogenase, *MPC* mitochondrial pyruvate carrier, *LDH* lactate dehydrogenase, *Glut* glucose transporter

due to an increase in lipoprotein lipase (LPL) activity in insulin-resistant [101], and diabetic animals [102, 103], although a consistent increase in LPL has not been found [102–106]. The uptake of fatty acids into cardiomyocytes is facilitated by the action of a number of fatty acid transporters (e.g. FAT/CD36, FABPpm, and FATPs) (Fig. 1). Translocation of FAT/CD36 to the sarcolemmal membrane is increased in the presence of insulin resistance and diabetes resulting in increased fatty acid uptake [96, 97, 107]. Increased expression and sarcolemmal localization of fatty acid transporters may also partially account for increased fatty acid supply and oxidation [108–110] (Fig. 2).

5.2 Alterations in the Intracellular Fate of Fatty Acids

This can also contribute to the high fatty acid oxidation rates in obesity and diabetes. Once transported into the cytosol, fatty acids are esterified to CoA by fatty acyl CoA synthetase (Fig. 1), forming long chain acyl CoA. Most of the long chain acyl CoAs is destined for mitochondrial fatty acid oxidation, but a small portion can be converted into intracellular lipid intermediates, such as TAG, phospholipids, diacylglycerol (DAG), and ceramide. To undergo ß-oxidation, the acyl groups from long chain acyl-CoA are transported into the mitochondria via a carnitine-dependent transport system (Fig. 1) involving carnitine palmitoyl transferase-1 (CPT-1). CPT-1 activity is controlled by malonyl CoA, a potent allosteric inhibitor of CPT-1) [111]. Malonyl CoA content, in turn, is controlled by its rate of turnover. Acetyl CoA carboxylase (ACC) catalyzes the synthesis of malonyl-CoA, whereas malonyl CoA decarboxylase (MCD) catalyzes its degradation. In diabetes malonyl CoA control of CPT-1 is decreased, due in part to an increased expression of MCD [112], resulting in increased mitochondrial uptake and oxidation of fatty acids.

5.3 Alterations in the Fatty Acid ß-Oxidative Pathway

This can also contribute to increased fatty acid oxidation in obesity and diabetes. In *db*/*db* mice, increased cardiac fatty acid oxidation [35, 43, 113, 114] is associated with a concomitant increase in the activity of enzymes of mitochondrial oxidation. This increase in fatty acid oxidative enzymes may be related to an increase in the transcriptional regulator PPARα, which increases fatty acid oxidative enzyme expression and produces a dramatic increase in fatty acid oxidation that has the potential to decrease cardiac efficiency [115]. Pharmacologically shifting the balance of oxidative metabolism from fatty acid oxidation towards glucose oxidation by targeting either (1) the cellular uptake of energy substrates, (2) transcriptional regulators of energy substrate metabolism, (3) mitochondrial fatty acid uptake, (4) mitochondrial fatty acid oxidation, and (5) glucose oxidation can improve the efficiency of ATP generation and hydrolysis (see for review [31]).

5.4 Acetylation Control of Cardiac Fatty Acid Oxidation in Insulin Resistance and Diabetes

Protein acetylation is an important dynamic/reversible post-translational modification involved in many cellular processes, including nuclear transcription, cell survival, apoptosis, and differentiation [116, 117]. Nuclear lysine acetylation has been extensively studied, and is linked to active gene transcription [118–120]. This post-translational modification is mediated by histone acetyltransferases (HATs) and is

reversed by histone deacetylases (HDACs). Both class 1 and class 2 HDACs play important roles in cardiac hypertrophy [116, 121–124]. Nuclear acetylation has an important role in regulating cardiac energy metabolism. For instance, PGC-1α and HIF-1α, important transcriptional regulators of genes involved in mitochondrial oxidative metabolism and glycolysis, are both under acetylation control [125–130].

Non-nuclear lysine acetylation has also emerged as an important post-translational regulator of many metabolic pathways [131–134]. This includes enzymes that are involved in mitochondrial metabolism and glycolysis and transcriptional regulation of glycolysis and mitochondrial oxidative metabolism [133–138]. Despite the recent identification of numerous acetylation sites on metabolic enzymes, the role of acetylation in regulating cardiac energy metabolism is still poorly understood. While it is generally thought that acetylation decreases enzyme activity, this is not always the case. A number of glycolytic enzymes appear to be activated by acetylation [133, 136, 138]. Acetylation of fatty acid oxidation enzymes is generally considered to inhibit fatty acid oxidation. For instance, Hirschey et al. [133, 139] proposed that acetylation inhibits liver fatty acid oxidation, via inhibition of the fatty acid oxidation enzyme, long chain acyl CoA dehydrogenase (LCAD). However, we recently showed that acetylation is actually associated with increased fatty acid oxidation in the heart. Increased acetylation of LCAD and hydroxyacyl CoA dehydrogenase (HACD) is associated with increased HACD activity under conditions where cardiac fatty acid oxidation is high. In support of this, Zhao et al. showed that acetylation of the hepatic fatty acid oxidation enzyme enoyl-CoA hydratase/3-HACD is associated with its activation [132]. Of importance, we have demonstrated that cardiac fatty acid oxidation rates are increased in SIRT3 ko mice, which occurs concomitant with a decreased glucose oxidation. The overall acetylation of myocardial proteins is enhanced in SIRT3 ko mice. Elevated acetylation of myocardial HCAD and LCAD are also evident, which is accompanied by an increased activity of LCAD. In agreement, a decrease in the acetylation of mitochondrial proteins has been reported in cells overexpressing SIRT3 [140, 141]. Further support for the concept that increased acetylation increases, rather than decreases, fatty acid oxidation was found in hindlimb muscle of fasted mice, where increased acetylation and fatty acid oxidation rates were observed [142]. Diaphragm muscle of SIRT3 ko mice also have increased fatty acid oxidation rates [142].

Multiple enzymes in the TCA cycle and ETC are also targets for acetylation. The effects of acetylation on these enzymes is poorly understood, but it is generally considered that acetylation decreases TCA cycle and ETC activity, thereby compromising mitochondrial ATP production [133, 139–141].

Another target of acetylation are enzymes in the insulin signaling and glycolytic pathway [142, 143], suggesting that alterations in acetylation may contribute to the insulin resistance seen in obesity, diabetes, and heart failure. A number of glycolytic enzymes are acetylated, and inhibition of glycolysis is associated with a reduction in SIRT1 expression [138]. Hepatic insulin resistance is also associated with reduced expression levels of SIRT1 [144–149]. Reduced SIRT1 expression also leads to reduced Akt activation and decreased insulin-induced IRS-2 tyrosine phosphorylation in several cell lines *in vitro* [150]. Conversely, SIRT1-mediated deacetylation of

Akt, and its upstream activator, phosphoinositide dependent kinase 1 (PDK1) promotes Akt activation [151]. Of importance is that low levels of SIRT1 expression negatively correlate with obesity and BMI in humans [152]. In obese mice, SIRT1 activation can also improve insulin sensitivity [153].

6 The Consequences of Altered Fatty Acid Oxidation in Obesity, Diabetes, and Heart Failure

6.1 Altered Insulin Signaling and Lipid Intermediate Accumulation

Increased myocardial uptake of fatty acids leads to accumulation of lipid metabolites, which can have a profound impact on insulin signaling and cardiac function. Diacylglycerol (DAG), and ceramides can activate kinases involved in the down-regulation of insulin action [154–158]. Activation of JNK-AP-1, IKK-NF-κB and PKC cascades by lipid intermediates has a negative feedback on insulin action, acting via serine phosphorylation of IRS-1 [159]. A negative relationship between the accumulation of intracellular lipids in skeletal muscle and insulin sensitivity has been reported in obesity in both humans [160] and rodents [161–163].

Long chain acyl CoA's (LC acyl CoA) are also potential mediators of insulin resistance [164], and elevated levels of LC acyl CoA have been associated with decreased glucose uptake in obese individuals [165]. Obesity promotes accumulation of LC acyl CoA in muscle, which is accompanied by insulin resistance. Studies have shown an inverse relationship between muscle LC acyl CoA content and insulin resistance [164, 166–170], although this relationship does not always hold [171].

Ceramide may also be a mediator of insulin resistance. Accumulation of ceramide occurs either by the hydrolysis of sphingomyelin [172] or by *de novo* synthesis from saturated fatty acids [173]. Ceramide decreases insulin-stimulated glucose uptake in skeletal muscle [174, 175], and inhibition of ceramide [176]. Interestingly, although cardiac ceramide content does not increase in obesity [4], the salutary effects of decreasing ceramide content in promoting insulin sensitivity in skeletal muscle may nonetheless be transferable to cardiac muscle. Ceramides inhibit insulin action via the inhibition of Akt phosphorylation [174, 175], while inhibition of ceramide synthesis restores phosphorylation of Akt in insulin-resistant myotubes [174].

DAG content is increased in muscle from insulin resistant rodents and humans [158, 177–179]. In human studies, accumulation of DAG in skeletal muscle of obese, and diabetic individuals is positively correlated with the increased activity of PKC-θ [180, 181], which can impair insulin signaling via serine phosphorylation of IRS-1 [158, 181].

Accumulation of lipids has been implicated as an important mediator of cardiac dysfunction [182]. The increased concentration of TAG in association with insulin

resistance is seen in hearts from obese humans and rodents, and genetically obese and type 2 diabetic rodents [176, 183–187]. Cardiac dysfunction in Zucker obese rats is positively correlated with the accumulation of myocardial TAG and ceramide [186]. Accumulation of ceramide in the rat heart following obesity has also been observed [188]. Cardiac overexpression of PPARγ in mice subjected to obesity also augments myocardial ceramide content [189], which is implicated in the development of insulin resistance and heart failure [190–192].

6.2 Incomplete Fatty Acid Oxidation in Obesity

Increases in fatty acid oxidation that exceed the ability of the mitochondria to metabolize its downstream products can lead to the failure of muscle to completely oxidize fatty acids, leading to the accumulation of acid soluble metabolites (markers of incomplete oxidation) [45, 80]. In contrast, increasing TCA cycle and ETC activity prevents incomplete fatty acid oxidation [80]. Indeed, increased fatty acid oxidation in the skeletal muscle and heart during high fat feeding contributes to the mismatch between β-oxidation and TCA cycle activity, leading to incomplete fatty acid oxidation [60, 193]. This is supported by the observation that intermediates of incomplete fatty acid oxidation accumulate in muscle from insulin-resistant animals, and that decreasing this accumulation can improve insulin sensitivity [45, 194].

In order for insulin resistance to develop, excess fatty acids have to enter the mitochondria [5], a concept supported by the observation that channeling excessive fats to storage in the form of TAG limits insulin resistance [183, 195]. Acylcarnitines, which are markers of incomplete oxidation, may contribute to the acylation and acetylation of mitochondrial proteins to alter their function [196]. We speculate that enhancing fatty acid oxidation does not increase insulin sensitivity. Rather, correcting the ‘mismatch’ between oxidation and TCA cycle activity by lowering β-oxidation may alleviate insulin resistance.

7 Conclusions

Heart failure associated with obesity and diabetes results in dramatic changes in cardiac energy metabolism. While overall mitochondrial energy production is decreased in the heart, fatty acid oxidation rates are markedly increased. This is associated with a decrease in glucose oxidation and a decrease in insulin stimulation of glucose metabolism. These metabolic changes are associated with a decrease in cardiac efficiency that can compromise cardiac function. As a result, inhibition of fatty acid oxidation in heart failure associated with obesity and diabetes has the potential to improve cardiac function and efficiency.

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