The Role of Incomplete Fatty Acid β-Oxidation in the Development of Cardiac Insulin Resistance

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Abstract As obesity is a significant risk factor for cardiovascular disease, there is a growing need to understand the precise mechanisms by which obesity and its associated dyslipidemia negatively affect the myocardium and lead to cardiac dysfunction. Current dogma suggests that obesity-associated dyslipidemia increases fatty acid delivery to the heart, which contributes to both excessive fatty acid uptake and subsequent fatty acid oxidation rates that ultimately result in the development of cardiac lipotoxicity and insulin resistance. However, recent evidence demonstrates that increased rates of incomplete fatty acid oxidation (mismatch between mitochondrial β-oxidation rates and tricarboxylic acid cycle activity) may also contribute to the progression of cardiac insulin resistance through inhibition of insulin-sensitive glucose oxidation, which will be the topic of discussion in this specific chapter.

Keywords Incomplete fatty acid β-oxidation • Fatty acid β-oxidation • Insulin resistance • Cardiac lipotoxicity • Cardiomyopathy • Type 2 diabetes • Obesity • Triacylglycerol • Diacylglycerol • Ceramide

1 Introduction

Cardiovascular disease is a major cause of morbidity and death in the world today. With recent advancements in evidence-based medicine, the overall management of patients with cardiovascular diseases has significantly improved. However, there are still a large number of patients who are ineligible or refractory to conventional treatment, and thus novel approaches to treat these patients are necessary.

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With the heart being the most metabolically demanding organ in the body, the optimization of cardiac energy metabolism appears to be one such novel approach. Indeed, alterations in fatty acid oxidation have been demonstrated in numerous cardiovascular pathologies, including ischemic heart disease, diabetic cardiomyopathy, and heart failure [1–3]. Furthermore, a multitude of studies in the past 20 years have illustrated that reversing these alterations in myocardial fatty acid metabolism can improve cardiac function and alleviate disease pathology [4–10]. As the individual chapters in this textbook will delineate in great detail the regulation of cardiac energy metabolism, it's contribution to the development and progression of various cardiovascular diseases such as ischemic heart disease and heart failure, this specific chapter aims to focus on the potential role of incomplete fatty acid β-oxidation in the heart as a mediator of cardiac insulin resistance.

2 Cardiac Energetics

In the healthy heart, virtually all (~95 %) ATP generated arises from mitochondrial oxidative phosphorylation, with the remainder derived from glycolysis. In cardiac muscle fatty acids account for the majority of oxidative energy metabolism (~60–80 %), while carbohydrate metabolism accounts for the remaining 20–40 %. The following section will briefly describe the processes of glucose and fatty acid metabolism in the myocardium.

2.1 Carbohydrate Metabolism

Glucose and lactate are the primary carbohydrates metabolized by the heart (*for in-depth review of the regulation of cardiac carbohydrate metabolism, please refer to Jaswal et al.* [2]). Glucose transporters (i.e. GLUT1/4) are responsible for glucose uptake into the cardiac myocyte, whereby glucose either undergoes anabolism to produce glycogen, or is catabolized for ATP production through both glycolysis and glucose oxidation. Glycolysis produces pyruvate and accounts for less than 10 % of the total ATP generated by the aerobic adult heart [1]. If glycolysis is coupled to glucose oxidation, the pyruvate produced from glycolysis will be transported into the mitochondria via the mitochondrial pyruvate carrier and subsequently converted into acetyl CoA by the enzymatic activity of pyruvate dehydrogenase (PDH).

2.2 Fatty Acid Metabolism

Fatty acids enter the cardiac myocyte via either passive diffusion or through a number of protein transporters such as the fatty acid translocase, CD36, or fatty acid transport proteins. Prior to either storage as triacylglycerol (TAG) or mitochondrial

fatty acid β-oxidation for energy production, these fatty acids must first be activated into fatty acyl CoA via fatty acyl CoA synthase, which converts a fatty acid into a fatty acyl CoA ester in an ATP-dependent manner (*for in-depth review of the regulation of cardiac fatty acid metabolism, please refer to Lopaschuk et al.* [3]). Because the inner mitochondrial membrane is impermeable to CoA esters, mitochondrial uptake of fatty acyl CoA requires a complex of proteins that relies on a carnitine-dependent shuttle system [11]. Carnitine palmitoyl-transferase 1 (CPT-1), which is the rate-limiting enzyme for mitochondrial fatty acid uptake and subsequent fatty acid β-oxidation, resides on the outer mitochondrial membrane and converts fatty acyl CoA esters into their corresponding fatty acylcarnitine moieties [12, 13]. The acylcarnitine is then transported into the mitochondrial matrix by carnitine translocase, and reconverted back into its corresponding fatty acyl CoA ester by CPT-2, which resides on the inner mitochondrial membrane's inner leaflet [3]. Fatty acyl CoA esters are sequentially oxidized within the mitochondrial matrix by the successive enzymatic actions of acyl CoA dehydrogenase, enoyl CoA hydratase, 3-hydroxyacyl CoA dehydrogenase, and 3-ketoacyl CoA thiolase. The process of fatty acid β-oxidation results in the progressive shortening of a fatty acyl CoA ester by two carbon units through liberation of acetyl CoA, while also producing the reducing equivalents, NADH and $FADH_2$, which act as electron donors for the electron transport chain, in order to fuel ATP synthesis via oxidative phosphorylation [14].

3 Insulin's Effect on Myocardial Metabolism

The heart is an insulin sensitive organ whereby internal GLUT4 transporters are translocated to the sarcolemmal membrane in response to insulin to facilitate glucose uptake (refer to Allard [15] for an extensive review on the effects of insulin on myocardial metabolism). Therefore, one of the primary functions of insulin in the heart is to stimulate glucose metabolism, which includes an increase in glucose uptake, glycogen synthesis, glycolysis and glucose oxidation (Fig. 1). Insulin's effects on glycolysis are due to activation of 6-phosphofructo-2-kinase (PFK-2), which increases fructose 2,6-bisphosphate, a potent stimulator of 6-phosphofructo-1-kinase (PFK-1), the rate-limiting enzyme of glycolysis [16]. Insulin also has positive effects on PDH activation, possibly via PDH phosphatase, which contributes to its overall effect to enhance glucose oxidation [17]. Moreover, as other chapters have highlighted the role of the Randle Cycle and the inverse relationship between fatty acid and glucose oxidation, insulin's ability to reduce fatty acid mobilization from adipose tissue reduces the delivery of fatty acids to the heart. This results in a subsequent reduction in myocardial fatty acid β-oxidation rates and decreases the inhibitory effects of fatty acid oxidation on PDH activity and glucose oxidation.

Although the heart's glycogen stores are not as large as those present in the skeletal muscle or liver, the mechanisms driving glycogen synthesis in the myocardium are very similar. Perfusion of rat hearts in the presence of insulin leads to the rapid dephosphorylation and activation of glycogen synthase [18]. This may be explained by the activation of phosphatidylinositide 3-kinase, which increases

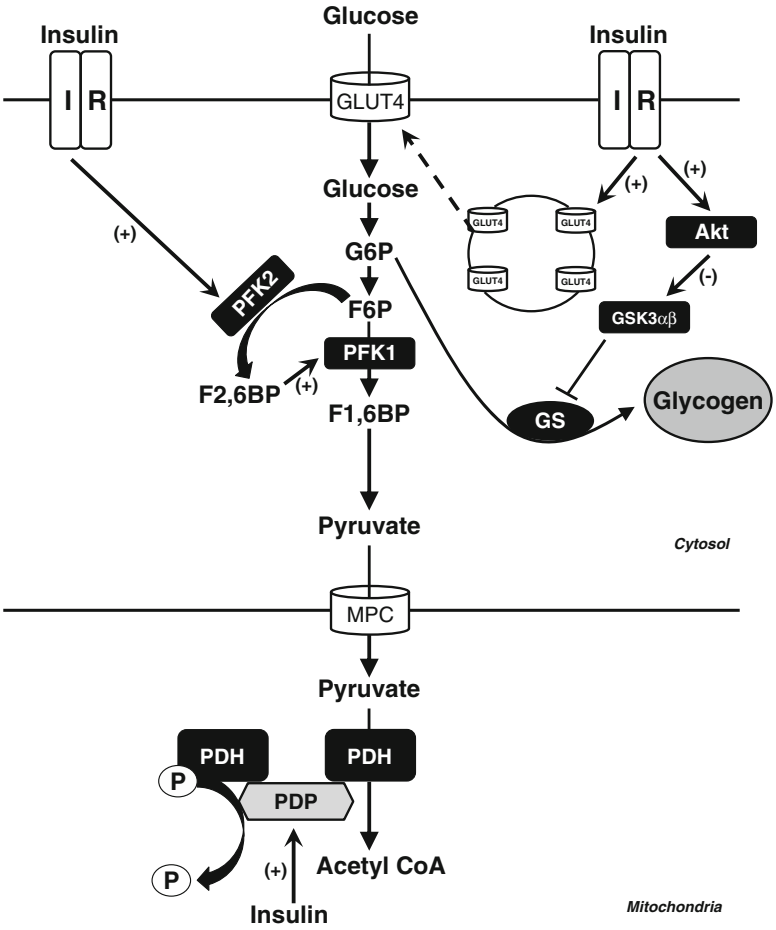

Fig. 1 Insulin and cardiac glucose metabolism. In the heart, insulin increases glucose uptake, glycolysis, glycogen synthesis, and glucose oxidation. Upon binding to its receptor at the sarcolemmal membrane, insulin activates Akt, which through a number of downstream mediators, ultimately results in the translocation of GLUT4 transporters from internalized vesicles to the membrane, thereby facilitating cellular glucose uptake. At the same time, activation of Akt relieves GSK3β-mediated inhibition of glycogen synthase, allowing glycogenesis to take place. Furthermore, insulin receptor activation results in the activation of PFK2, which increases fructose 2,6-bisphosphate generation, thereby stimulating 6-phosphofructo-1-kinase and subsequently increasing glycolysis rates. Last, insulin has also been postulated to increase PDH activity and subsequent glucose oxidation rates, possibly by direct actions to increase PDH phosphatase activity, which relieves phosphorylation-mediated inhibition of PDH activity. *IR* insulin receptor, *G6P* glucose-6-phosphate, *F6P* fructose-6-phosphate, *F1,6BP* fructose-1,6-bisphosphate, *F2,6BP* fructose-2,6-bisphosphate, *PFK1* 6-phosphofructo-1-kinase, *PFK2* 6-phosphofructo-2-kinase, *GS* glycogen synthase, *GSK3* glycogen synthase kinase 3, *MPC* mitochondrial pyruvate carrier, *PDH* pyruvate dehydrogenase, *PDP* PDH phosphatse

phosphatidylinositol (3,4,5) trisphosphate production, leading to activation of phosphoinositide-dependent kinase 1 and the subsequent activation of Akt. Active Akt phosphorylates and inactivates glycogen synthase kinase α/β (GSK3α/β), allowing glycogen synthase to remain in an active dephosphorylated state, resulting in increased glycogen synthesis [19].

In muscle, insulin can inhibit CPT-1 and subsequent fatty acid β-oxidation rates [20], and it has been hypothesized that this mechanism also occurs in the heart, though conflicting opinions exist in regards to this manner [15, 21, 22]. Direct changes in malonyl CoA (a potent endogenous inhibitor of CPT-1) levels have been proposed to account for the rapid effect of insulin on CPT-1 activity, which would likely arise from increased acetyl CoA carboxylase (ACC) activity, the only source of malonyl CoA in mammalian cells. In support of this, isolated working heart perfusions in the absence of insulin demonstrate a lack of effect of citrate on ACC activity [23]. On the other hand, isolated working heart perfusions in the presence of insulin show a positive allosteric effect of citrate on ACC activity [24]. Insulin has also been shown to inhibit AMPK, a major kinase whose activation leads to increased rates of fatty acid oxidation in both heart and skeletal muscle [25, 26]. However, this effect of insulin is unlikely to play a role in reducing fatty acid β-oxidation rates in the insulin resistant heart, as studies have demonstrated a loss of insulin-dependent AMPK inhibition in the presence of high free fatty acid levels in the perfusate, which would mimic circulating free fatty acid levels seen in insulin resistant and type 2 diabetic patients [27].

4 Insulin Resistance

Insulin resistance is the failure of insulin to mediate a normal insulin-type response from insulin-sensitive tissues, resulting in dysregulated blood glucose homeostasis. It involves decreased glucose uptake into the skeletal muscle, heart, and adipose tissue, and increased hepatic glucose production, all of which contribute to the elevation in glycemia observed in insulin resistant patients. As the skeletal muscle serves as the "sink" for glucose disposal in response to insulin, numerous studies investigating the molecular mechanisms responsible for causing insulin resistance have focused their efforts in this tissue. Although there has been no true discovery to date as to what specific factor causes insulin resistance, there has been vast progress in regards to potential culprits of this devastating condition. Some of these include inflammatory responses associated with increased circulating tumor necrosis factor alpha and other cytokines [28–30], increased intramyocellular ceramide production [31, 32], oxidative stress [33, 34], intramyocellular lipid metabolite accumulation (TAG, long chain acyl CoA, and DAG) [35, 36], and hyperlipidemia [37]. While there are many different proposed candidates for what initially causes insulin resistance, common cellular mechanisms do exist, primarily involving a failure of insulin to increase insulin receptor substrate-associated phosphatidylinositide

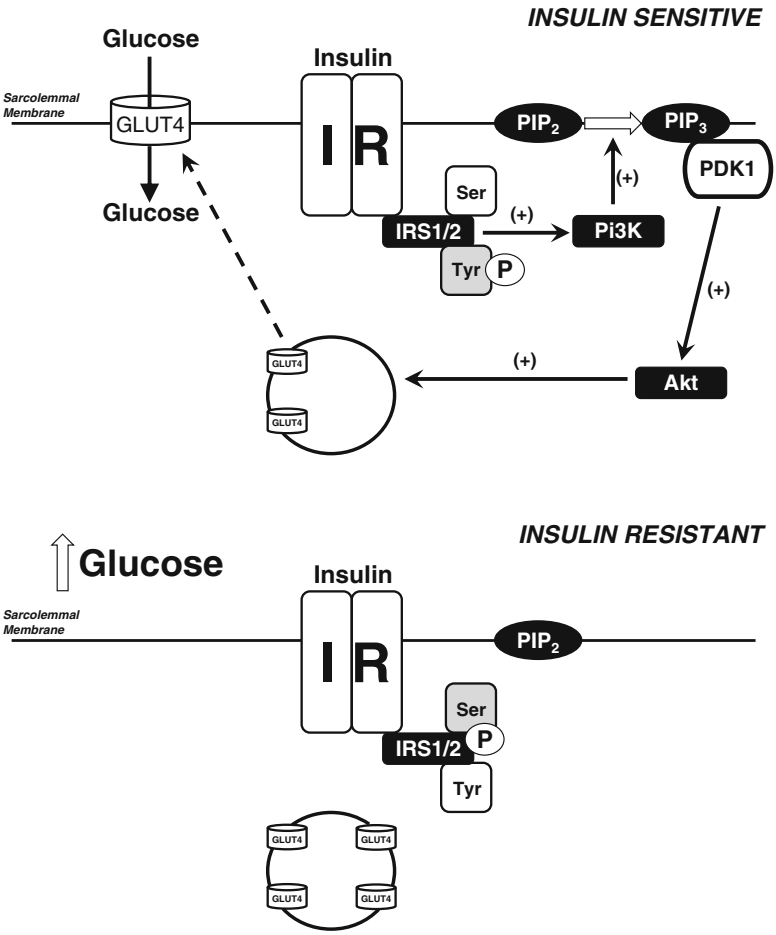

Fig. 2 Defects in insulin signaling during insulin resistance. During normal insulin signaling, insulin receptor activation results in tyrosine phosphorylation of IRS1/2, which results in activation of PI3K. A number of downstream signaling events ultimately result in activation of Akt and subsequent translocation of GLUT4 transporters from internalized vesicles to the membrane, thereby facilitating cellular glucose uptake. It has been proposed that during insulin resistance, serine phosphorylation of IRS1/2 somehow interferes with tyrosine phosphorylation of IRS1/2, which inhibits IRS1/2's ability to recruit and activate PI3K, preventing GLUT4 translocation and subsequent glucose uptake. *IR* insulin receptor, *PDK1* phosphoinositide-dependent kinase 1, *PI3K* phosphatidylinositide 3-kinase, PIP_2 phosphatidylinositol 3,5-bisphosphate, PIP_2 phosphatidylinositide 3-phosphate, *Ser* serine, *Tyr* tyrosine

3-kinase activity [30, 35, 38]. This results in reduced generation of phosphatidylinositol (3,4,5) trisphosphate and thereby prevents activation of phosphoinositide-dependent kinase 1, which impairs insulin-stimulated GLUT4 translocation to the sarcolemmal membrane (Fig. 2).

While insulin resistance is primarily discussed in relation to defects in skeletal muscle signaling, one must not forget that the heart is also a muscle, and many of

the proposed factors that cause insulin resistance also inflict many negative effects on cardiac muscle [39]. However, there is mounting evidence that there is little to no loss of insulin sensitivity in the hearts from patients with type 2 diabetes [3]. Studies measuring the effects of hyperinsulinemia on myocardial glucose uptake demonstrate either minor or a lack of insulin resistance in type 2 diabetic patients compared with nondiabetic control subjects [40, 41]. This is particularly evident when circulating free fatty acid levels are matched [42]. Similarly, in animal studies, utilization of a genetic mouse model of type 2 diabetes supports the concept that myocardial insulin responsiveness is relatively intact in type 2 diabetes [43, 44]. This is in clear contrast to skeletal muscle and adipose tissue, where insulin resistance is a significant contributor to the observed elevations in circulating glucose and free fatty acid concentrations. The constant exposure of the heart to high free fatty acid and glucose levels could exert toxic effects (glucolipotoxicity) from the generation of harmful derivatives of glucose and lipid metabolism [45, 46]. Thus, although the heart may be less vulnerable to insulin resistance than skeletal muscle, systemic insulin resistance may still exert profound negative effects on the myocardium through the toxic effects of excess substrate [45, 46].

On the other hand, with regards to cardiac glucose metabolism, it is becoming clear that the most robust alterations take place at the level of glucose oxidation in the insulin resistant heart, and not at the level of glucose uptake and glycolysis [9, 47]. The following section will discuss in depth how the incomplete β-oxidation of fatty acids may contribute towards the pathogenesis of cardiac insulin resistance at the level of glucose oxidation, and whether this may represent a novel target to improve altered cardiac energetics in the setting of obesity and type 2 diabetes.

5 Incomplete Fatty Acid β-Oxidation

The complete oxidation of a fatty acyl CoA ester encompasses the production of acetyl CoA continuously until the fatty acyl chain is catabolized into its final four carbons, with the final β-oxidation spiral liberating the last two acetyl CoA molecules. As mentioned in the previous section, during the complete oxidation of a fatty acyl CoA ester, these acetyl CoA molecules are subsequently metabolized via the tricarboxylic acid (TCA) Cycle, generating the reducing equivalents NADH and $FADH_2$, which are utilized by the electron transport chain to fuel ATP synthesis via oxidative phosphorylation. If the TCA cycle cannot keep up with the incoming acetyl CoA being generated via mitochondrial fatty acid β-oxidation, the fatty acyl CoA esters will end up being incompletely oxidized (Fig. 3). As total CoA and carnitine levels are similar in the matrix space, and with CPT-2's transferase reaction maintained at a thermodynamic equilibrium of 0.45, as fatty acyl CoA esters are incompletely oxidized and various mitochondrial acyl CoAs accumulate, their respective acylcarnitine counterparts will also accumulate in the mitochondria [48]. Therefore, the use of targeted lipid profiling metabolomics to quantify various carbon chain length acylcarnitines has become a powerful tool to assess the status of incomplete fatty acid β-oxidation in peripheral tissues such as the muscle and heart [49].

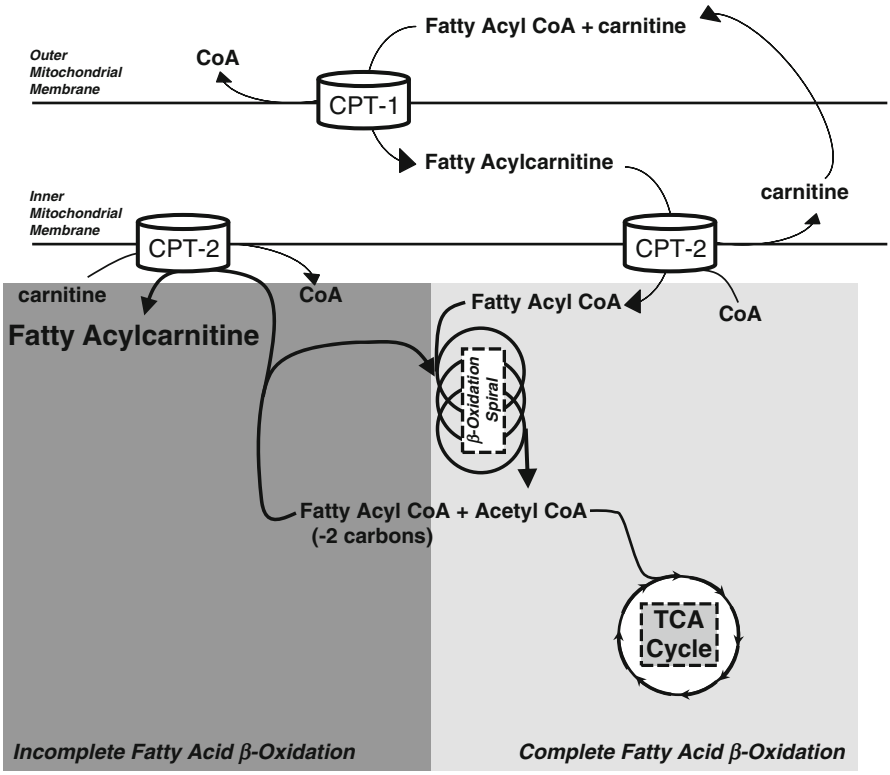

Fig. 3 Incomplete fatty acid β-oxidation. If the TCA cycle cannot sustain metabolism of the acetyl CoA being generated via mitochondrial fatty acid β-oxidation, the fatty acyl CoA esters will end up being incompletely oxidized. Because CoA and carnitine concentrations are similar in the mitochondrial matrix space, and with CPT-2's transferase reaction maintained at a thermodynamic equilibrium of 0.45, if a fatty acyl CoA ester is incompletely oxidized and mitochondrial fatty acyl CoA esters accumulate, CPT-2 will catalyze the reconversion of the accumulated acyl CoAs back into their respective acylcarnitine moieties

5.1 Incomplete Fatty Acid β-Oxidation and Skeletal Muscle Insulin Resistance

Elegant studies by Muoio and colleagues have demonstrated a significant role for excessive incomplete fatty acid β-oxidation rates in the development of skeletal muscle insulin resistance in response to underlying obesity. In cultured L6 rat skeletal muscle myotubes, increasing fatty acid concentrations increases incomplete fatty acid β-oxidation rates, which can be overcome via overexpression of peroxisome proliferator-activated receptor-γ-coactivator 1α [50]. Moreover, obese rats, mice, and Zucker diabetic fatty rats exhibit significant insulin resistance that is associated with a marked increase in the accumulation of a number of long chain

acylcarnitines in gastrocnemius muscle, combined with a reduction in a number of intermediates of the TCA cycle [51]. These findings are consistent with elevated incomplete fatty acid β-oxidation rates in insulin resistant skeletal muscle. Of interest, mice deficient for malonyl CoA decarboxylase (MCD−/−) exhibit reduced incomplete fatty acid β-oxidation rates due to reduced CPT-1 activity and subsequent mitochondrial fatty acid uptake, and are protected against obesity-induced skeletal muscle insulin resistance [51]. Similarly, treatment of diet-induced obese mice with the CPT-1 inhibitor, oxfenicine, protects mice against skeletal muscle insulin resistance and glucose intolerance [52], and this is associated with a reduction in myocyte incomplete fatty acid oxidation rates (unpublished observations). On the contrary, mice with a muscle-specific deficiency of carnitine acetyltransferase (CrAT) demonstrate an elevation in long chain acylcarnitines in gastrocnemius muscle and are glucose intolerant [53]. Furthermore, muscle-specific CrAT deficient mice exhibit metabolic inflexibility, as they are unable to switch to carbohydrate oxidation during the transition from fasting to feeding [53]. These findings appear clinically relevant, as studies in obese and type 2 diabetic humans have recapitulated observations of acylcarnitine accumulation and incomplete fatty acid β-oxidation in muscle [54, 55]. Furthermore, obese patient-derived primary human skeletal muscle myocytes cultured in the presence of lipolytically active adipocytes demonstrate a metabolic signature consistent with incomplete fatty acid β-oxidation, as medium and long chain acylcarnitines accumulated compared to myocytes cultured in the absence of adipocytes [56]. Intriguingly, treatment with the CPT-1 inhibitor, etomoxir, reduced the detrimental effects of lipolytically active adipocytes on glucose oxidation rates in obese patient-derived primary human skeletal muscle myocytes [56].

While the aforementioned studies support the notion that incomplete fatty acid β-oxidation negatively impacts skeletal muscle insulin sensitivity and subsequent carbohydrate utilization, the mechanism(s) responsible for this effect remain to be elucidated. Moreover, whether the accumulation of long chain acylcarnitines, which are often used as an index to identify that an increase in incomplete fatty acid β-oxidation rates is taking place in the muscle, can actually have direct cellular effects to inhibit insulin sensitivity is unknown. It has been suggested that acylcarnitine accumulation does not directly mediate insulin resistance, but rather may reflect a failed attempt to alleviate oxidative stress caused by mitochondrial lipid overload [57]. On the other hand, in recent years our appreciation of protein acylation/acetylation has grown considerably, with alterations in protein acylation/acetylation now thought to play a significant role in regulating mitochondrial function in the setting of obesity-related metabolic diseases [58]. Indeed, results from mass spectrometry-based proteomics have suggested that at least 20 % of the mitochondrial proteome is acetylated. Furthermore, the NAD^+-dependent deacetylase, sirtuin 3 (Sirt3), has been demonstrated to acetylate PDH, resulting in an inhibition of PDH activity [59]. In mice deficient for Sirt3, PDH in muscle is hyperacetylated, which results in a subsequent reduction in glucose oxidation and impairs metabolic flexibility during the fasting to feeding transition [59]. Thus, it is possible that the accumulation of acylcarnitines in the mitochondria may provide surplus acetyl residues

and contribute to the elevated acetylation of PDH and reduced glucose oxidation rates observed in the muscle in response to obesity-associated insulin resistance. As mentioned previously, muscle-specific CrAT deficient mice exhibit long chain acylcarnitine accumulation in muscle and are markedly insulin resistant, which is associated with a reduction in PDH activity [53]. Moreover, overexpression of CrAT in primary cultured human skeletal myocytes protects against fatty acid-induced PDH inhibition and improves glucose uptake [60]. Hence, CrAT activity may play a critical role in protecting PDH activity against incomplete fatty acid β-oxidation and subsequent mitochondrial lipid stress. Whether CrAT activity is altered in response to overnutrition and obesity remains to be determined.

5.2 Incomplete Fatty Acid β-Oxidation and Cardiac Insulin Resistance

Unlike the muscle, the heart is not subject to voluntary contraction and must continuously beat in order to deliver blood, oxygen, and nutrients to the rest of the body's organs for proper function. Thus, incomplete fatty acid β-oxidation is less likely to occur in the heart than the skeletal muscle, as there is constant demand on the TCA cycle to generate NADH and $FADH_2$ for oxidative phosphorylation to fuel ventricular contraction. Indeed, studies in the intact, isolated working heart demonstrate equivalent palmitate oxidation rates when palmitate is labeled with either [U-^{14}C], [1-^{14}C], or [9,10-^{3}H] palmitate [61–63]. However, these studies in the intact isolated heart are only measuring the metabolism of a single, exogenously supplied fatty acid substrate, and do not account for oxidation of endogenously supplied fatty acids arising from TAG mobilization. Despite palmitic acid being the most abundant plasma saturated fatty acid, oleic acid circulates at even higher concentrations in the plasma. Regardless, at equivalent and noncompeting concentrations, palmitate and oleate are oxidized at similar rates by the isolated working aerobic rat heart [3]. Whether there are alterations in the complete oxidation of fatty acids in the heart during the development and progression of various pathologies such as angina pectoris remains to be determined. Of interest, isolated working heart studies demonstrate similar palmitate oxidation rates between hearts from lean and obese (12 weeks of unrestricted access to a 60 % lard diet) mice [9]. In contrast, using gas chromatography–mass spectrometry targeted metabolomics to obtain a snap shot of in vivo fatty acid myocardial metabolism through quantification of acylcarnitines revealed more comprehensive information, as a number of long chain acylcarnitines accumulated in hearts from obese mice compared to their lean counterparts [9]. These findings are consistent with an elevation in myocardial incomplete fatty acid β-oxidation rates in the setting of obesity.

As alluded to in previous sections, the effect of insulin resistance on the myocadium appears to be most apparent at the level of insulin-stimulated glucose oxidation, and not at the level of glucose uptake and glycolysis [9, 47]. Indeed, studies in MCD−/− mice, a mouse model that demonstrates reduced incomplete fatty acid

β-oxidation rates in skeletal muscle due to reduced CPT-1 activity and subsequent mitochondrial fatty acid uptake [64], are resistant to the effects of obesity to reduce myocardial PDH activity and impair insulin-stimulated glucose oxidation [9]. Paralleling findings in skeletal muscle, metabolic profiling in hearts from obese MCD−/− mice demonstrate a marked reduction in the accumulation of a number of long chain acylcarnitines, indicative of reduced incomplete fatty acid β-oxidation rates [9]. These findings suggest that MCD inhibition or reducing mitochondrial fatty acid uptake to limit incomplete fatty acid β-oxidation rates may have clinical utility for reversing the effects of obesity on cardiac glucose oxidation.

It is well established that obesity increases one's risk for heart failure [65]. With heart failure being associated with impaired energetics and reductions in mitochondrial function [2], it will be important to ascertain whether elevations in myocardial incomplete fatty acid β-oxidation rates contribute to the high prevalence of heart failure in obese patients. Indeed, studies investigating chronic ischemia-induced heart failure demonstrate a significant protection against adverse left ventricular remodeling and improved left ventricular ejection fraction in MCD−/− mice compared to their wild type littermates at 4 weeks following permanent left anterior descending coronary artery occlusion [7]. However, whether the reduced incomplete fatty acid β-oxidation rates observed in hearts from MCD−/− mice plays a role in this cardioprotection against heart failure remains to be determined.

6 Conclusions

Studies exploring the alterations in myocardial fatty acid metabolism in cardiovascular disease have experienced a significant resurgence in the past decade. This is due in part to the obesity epidemic that now plagues our population, as obesity is a significant risk factor for cardiovascular diseases such as heart failure, and one of the most immediate effects of obesity on the heart involves increased delivery of fatty acids to the myocardium. Although studies suggest that the healthy heart for most part will completely oxidize the fatty acids it extracts for the purposes of energy production to sustain contractile function, recent findings illustrate at least in obesity, that the heart begins to exhibit increased rates of incomplete fatty acid β-oxidation, and this is associated with reductions in insulin-stimulated glucose oxidation rates. As the most potent effects of obesity on cardiac insulin sensitivity appear to take place at the level of glucose oxidation and not glucose uptake or glycolysis, it will be important for future research to delineate the mechanism(s) by which incomplete fatty acid β-oxidation impairs glucose oxidation. Such findings may lead to the development of new targets to alleviate obesity-associated cardiac insulin resistance.

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References

1. Ussher JR, Lopaschuk GD (2006) Clinical implications of energetic problems in cardiovascular disease. Heart Metab 32:9–17
2. Jaswal JS, Keung W, Wang W et al (2011) Targeting fatty acid and carbohydrate oxidation–a novel therapeutic intervention in the ischemic and failing heart. Biochim Biophys Acta 1813:1333–1350
3. Lopaschuk GD, Ussher JR, Folmes CD et al (2010) Myocardial fatty acid metabolism in health and disease. Physiol Rev 90:207–258
4. Dyck JR, Cheng JF, Stanley WC et al (2004) Malonyl coenzyme a decarboxylase inhibition protects the ischemic heart by inhibiting fatty acid oxidation and stimulating glucose oxidation. Circ Res 94:e78–e84
5. Dyck JR, Hopkins TA, Bonnet S et al (2006) Absence of malonyl coenzyme A decarboxylase in mice increases cardiac glucose oxidation and protects the heart from ischemic injury. Circulation 114:1721–1728
6. Liu Q, Docherty JC, Rendell JC et al (2002) High levels of fatty acids delay the recovery of intracellular pH and cardiac efficiency in post-ischemic hearts by inhibiting glucose oxidation. J Am Coll Cardiol 39:718–725
7. Masoud WG, Ussher JR, Wang W et al (2013) Failing mouse hearts utilize energy inefficiently and benefit from improved coupling of glycolysis and glucose oxidation. Cardiovasc Res. doi:10.1093/cvr/cvt216
8. Mori J, Basu R, McLean BA et al (2012) Agonist-induced hypertrophy and diastolic dysfunction are associated with selective reduction in glucose oxidation: a metabolic contribution to heart failure with normal ejection fraction. Circ Heart Fail 5:493–503
9. Ussher JR, Koves TR, Jaswal JS et al (2009) Insulin-stimulated cardiac glucose oxidation is increased in high-fat diet-induced obese mice lacking malonyl CoA decarboxylase. Diabetes 58:1766–1775
10. Ussher JR, Wang W, Gandhi M et al (2012) Stimulation of glucose oxidation protects against acute myocardial infarction and reperfusion injury. Cardiovasc Res 94:359–369
11. Murthy MS, Pande SV (1984) Mechanism of carnitine acylcarnitine translocase-catalyzed import of acylcarnitines into mitochondria. J Biol Chem 259:9082–9089
12. Murthy MS, Pande SV (1987) Some differences in the properties of carnitine palmitoyltransferase activities of the mitochondrial outer and inner membranes. Biochem J 248:727–733
13. Murthy MS, Pande SV (1987) Malonyl-CoA binding site and the overt carnitine palmitoyltransferase activity reside on the opposite sides of the outer mitochondrial membrane. Proc Natl Acad Sci U S A 84:378–382
14. Ussher JR, Jaswal JS, Lopaschuk GD (2012) Pyridine nucleotide regulation of cardiac intermediary metabolism. Circ Res 111:628–641. doi:10.1161/CIRCRESAHA.111.246371
15. Brownsey RW, Boone AN, Allard MF (1997) Actions of insulin on the mammalian heart: metabolism, pathology and biochemical mechanisms. Cardiovasc Res 34:3–24
16. Hue L, Beauloye C, Marsin AS et al (2002) Insulin and ischemia stimulate glycolysis by acting on the same targets through different and opposing signaling pathways. J Mol Cell Cardiol 34:1091–1097
17. Hughes WA, Denton RM (1976) Incorporation of 32Pi into pyruvate dehydrogenase phosphate in mitochondria from control and insulin-treated adipose tissue. Nature 264:471–473
18. Adolfsson S, Isaksson O, Hjalmarson A (1972) Effect of insulin on glycogen synthesis and synthetase enzyme activity in the perfused rat heart. Biochim Biophys Acta 279:146–156
19. Mora A, Sakamoto K, McManus EJ, Alessi DR (2005) Role of the PDK1-PKB-GSK3 pathway in regulating glycogen synthase and glucose uptake in the heart. FEBS Lett 579: 3632–3638
20. Sidossis LS, Stuart CA, Shulman GI et al (1996) Glucose plus insulin regulate fat oxidation by controlling the rate of fatty acid entry into the mitochondria. J Clin Invest 98:2244–2250

21. Cook GA, Gamble MS (1987) Regulation of carnitine palmitoyltransferase by insulin results in decreased activity and decreased apparent Ki values for malonyl-CoA. J Biol Chem 262:2050–2055
22. Hudson EK, Liu MH, Buja LM, McMillin JB (1995) Insulin-associated changes in carnitine palmitoyltransferase in cultured neonatal rat cardiac myocytes. J Mol Cell Cardiol 27:599–613
23. Saddik M, Gamble J, Witters LA, Lopaschuk GD (1993) Acetyl-CoA carboxylase regulation of fatty acid oxidation in the heart. J Biol Chem 268:25836–25845
24. Kudo N, Barr AJ, Barr RL, Desai S, Lopaschuk GD (1995) High rates of fatty acid oxidation during reperfusion of ischemic hearts are associated with a decrease in malonyl-CoA levels due to an increase in 5'-AMP-activated protein kinase inhibition of acetyl-CoA carboxylase. J Biol Chem 270:17513–17520
25. Dyck JR, Lopaschuk GD (2006) AMPK alterations in cardiac physiology and pathology: enemy or ally? J Physiol 574:95–112
26. Kiens B (2006) Skeletal muscle lipid metabolism in exercise and insulin resistance. Physiol Rev 86:205–243
27. Folmes CD, Clanachan AS, Lopaschuk GD (2006) Fatty acids attenuate insulin regulation of 5'-AMP-activated protein kinase and insulin cardioprotection after ischemia. Circ Res 99:61–68
28. Ruan H, Lodish HF (2003) Insulin resistance in adipose tissue: direct and indirect effects of tumor necrosis factor-alpha. Cytokine Growth Factor Rev 14:447–455
29. Rosen ED, Spiegelman BM (2006) Adipocytes as regulators of energy balance and glucose homeostasis. Nature 444:847–853
30. Steinberg GR, Michell BJ, van Denderen BJ et al (2006) Tumor necrosis factor alpha-induced skeletal muscle insulin resistance involves suppression of AMP-kinase signaling. Cell Metab 4:465–474
31. Zierath JR (2007) The path to insulin resistance: paved with ceramides? Cell Metab 5:161–163
32. Pickersgill L, Litherland GJ, Greenberg AS et al (2007) Key role for ceramides in mediating insulin resistance in human muscle cells. J Biol Chem 282(17):12583–12589
33. Evans JL, Maddux BA, Goldfine ID (2005) The molecular basis for oxidative stress-induced insulin resistance. Antioxid Redox Signal 7:1040–1052
34. Evans JL, Goldfine ID, Maddux BA, Grodsky GM (2003) Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction? Diabetes 52:1–8
35. Kim JK, Gimeno RE, Higashimori T et al (2004) Inactivation of fatty acid transport protein 1 prevents fat-induced insulin resistance in skeletal muscle. J Clin Invest 113:756–763
36. Petersen KF, Shulman GI (2006) Etiology of insulin resistance. Am J Med 119:S10–S16
37. Kahn SE, Hull RL, Utzschneider KM (2006) Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 444:840–846
38. Dresner A, Laurent D, Marcucci M et al (1999) Effects of free fatty acids on glucose transport and IRS-1-associated phosphatidylinositol 3-kinase activity. J Clin Invest 103:253–259
39. Ussher JR, Lopaschuk GD (2013) Cardiac insulin resistance: it's sweeter than you think. Endocrinology 154:2575–2578
40. Paternostro G, Camici PG, Lammerstma AA et al (1996) Cardiac and skeletal muscle insulin resistance in patients with coronary heart disease. A study with positron emission tomography. J Clin Invest 98:2094–2099
41. Utriainen T, Takala T, Luotolahti M et al (1998) Insulin resistance characterizes glucose uptake in skeletal muscle but not in the heart in NIDDM. Diabetologia 41:555–559
42. Jagasia D, Whiting JM, Concato J et al (2001) Effect of non-insulin-dependent diabetes mellitus on myocardial insulin responsiveness in patients with ischemic heart disease. Circulation 103:1734–1739
43. Hafstad AD, Solevag GH, Severson DL et al (2006) Perfused hearts from Type 2 diabetic (db/db) mice show metabolic responsiveness to insulin. Am J Physiol Heart Circ Physiol 290:H1763–H1769

44. McNulty PH (2006) Metabolic responsiveness to insulin in the diabetic heart. Am J Physiol Heart Circ Physiol 290:H1749–H1751
45. Chess DJ, Stanley WC (2008) Role of diet and fuel overabundance in the development and progression of heart failure. Cardiovasc Res 79:269–278. doi:10.1093/cvr/cvn074
46. Taegtmeyer H, Stanley WC (2011) Too much or not enough of a good thing? Cardiac glucolipotoxicity versus lipoprotection. J Mol Cell Cardiol 50:2–5
47. Zhang L, Ussher JR, Oka T et al (2011) Cardiac diacylglycerol accumulation in high fat-fed mice is associated with impaired insulin-stimulated glucose oxidation. Cardiovasc Res 89:148–156
48. Idell-Wenger JA, Grotyohann LW, Neely JR (1978) Coenzyme A and carnitine distribution in normal and ischemic hearts. J Biol Chem 253:4310–4318
49. Bain JR, Stevens RD, Wenner BR et al (2009) Metabolomics applied to diabetes research: moving from information to knowledge. Diabetes 58:2429–2443
50. Koves TR, Li P, An J et al (2005) Peroxisome proliferator-activated receptor-gamma co-activator 1alpha-mediated metabolic remodeling of skeletal myocytes mimics exercise training and reverses lipid-induced mitochondrial inefficiency. J Biol Chem 280:33588–33598
51. Koves TR, Ussher JR, Noland RC et al (2008) Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. Cell Metab 7:45–56
52. Keung W, Ussher JR, Jaswal JS et al (2013) Inhibition of carnitine palmitoyltransferase-1 activity alleviates insulin resistance in diet-induced obese mice. Diabetes 62:711–720
53. Muoio DM, Noland RC, Kovalik JP et al (2012) Muscle-specific deletion of carnitine acetyltransferase compromises glucose tolerance and metabolic flexibility. Cell Metab 15:764–777
54. Mihalik SJ, Goodpaster BH, Kelley DE et al (2010) Increased levels of plasma acylcarnitines in obesity and type 2 diabetes and identification of a marker of glucolipotoxicity. Obesity (Silver Spring) 18:1695–1700
55. Adams SH, Hoppel CL, Lok KH et al (2009) Plasma acylcarnitine profiles suggest incomplete long-chain fatty acid beta-oxidation and altered tricarboxylic acid cycle activity in type 2 diabetic African-American women. J Nutr 139:1073–1081
56. Kovalik JP, Slentz D, Stevens RD et al (2011) Metabolic remodeling of human skeletal myocytes by cocultured adipocytes depends on the lipolytic state of the system. Diabetes 60:1882–1893
57. Muoio DM, Neufer PD (2012) Lipid-induced mitochondrial stress and insulin action in muscle. Cell Metab 15:595–605
58. Hirschey MD, Shimazu T, Jing E et al (2011) SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. Mol Cell 44: 177–190
59. Jing E, O'Neill BT, Rardin MJ et al (2013) Sirt3 regulates metabolic flexibility of skeletal muscle through reversible enzymatic deacetylation. Diabetes 62:3404–3417
60. Noland RC, Koves TR, Seiler SE et al (2009) Carnitine insufficiency caused by aging and overnutrition compromises mitochondrial performance and metabolic control. J Biol Chem 284:22840–22852
61. Lopaschuk GD, Hansen CA, Neely JR (1986) Fatty acid metabolism in hearts containing elevated levels of CoA. Am J Physiol 250:H351–H359
62. Lopaschuk GD, Spafford MA, Davies NJ, Wall SR (1990) Glucose and palmitate oxidation in isolated working rat hearts reperfused after a period of transient global ischemia. Circ Res 66:546–553
63. Saddik M, Lopaschuk GD (1991) Myocardial triglyceride turnover and contribution to energy substrate utilization in isolated working rat hearts. J Biol Chem 266:8162–8170
64. Ussher JR, Lopaschuk GD (2008) The malonyl CoA axis as a potential target for treating ischaemic heart disease. Cardiovasc Res 79:259–268
65. Kenchaiah S, Evans JC, Levy D et al (2002) Obesity and the risk of heart failure. N Engl J Med 347:305–313