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Review

Targeting fatty acid and carbohydrate oxidation — A novel therapeutic intervention in the ischemic and failing heart☆

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ABSTRACT

Cardiac ischemia and its consequences including heart failure, which itself has emerged as the leading cause of morbidity and mortality in developed countries are accompanied by complex alterations in myocardial energy substrate metabolism. In contrast to the normal heart, where fatty acid and glucose metabolism are tightly regulated, the dynamic relationship between fatty acid β-oxidation and glucose oxidation is perturbed in ischemic and ischemic–reperfused hearts, as well as in the failing heart. These metabolic alterations negatively impact both cardiac efficiency and function. Specifically there is an increased reliance on glycolysis during ischemia and fatty acid β-oxidation during reperfusion following ischemia as sources of adenosine triphosphate (ATP) production. Depending on the severity of heart failure, the contribution of overall myocardial oxidative metabolism (fatty acid β-oxidation and glucose oxidation) to adenosine triphosphate production can be depressed, while that of glycolysis can be increased. Nonetheless, the balance between fatty acid β-oxidation and glucose oxidation is amenable to pharmacological intervention at multiple levels of each metabolic pathway. This review will focus on the pathways of cardiac fatty acid and glucose metabolism, and the metabolic phenotypes of ischemic and ischemic/reperfused hearts, as well as the metabolic phenotype of the failing heart. Furthermore, as energy substrate metabolism has emerged as a novel therapeutic intervention in these cardiac pathologies, this review will describe the mechanistic bases and rationale for the use of pharmacological agents that modify energy substrate metabolism to improve cardiac function in the ischemic and failing heart. This article is part of a Special Issue entitled: Mitochondria and Cardioprotection.

1. Introduction

The high energy requirements of the myocardium are evidenced by the high rates of adenosine triphosphate (ATP) synthesis and hydrolysis. Myocardial ATP stores are relatively low compared to the amount of ATP required to sustain cardiac contraction, basal metabolism, and ionic homeostasis. As a result, there is a nearly complete turnover of the myocardial ATP pool every 10 s [1], with the heart cycling approximately 6 kg of ATP on a daily basis [2]. To meet these high energy demands, the normal heart possesses a high degree of metabolic flexibility, which is demonstrated by its ability to utilize various energy substrates including fatty acids, glucose, lactate, and ketone bodies to generate ATP. The contribution of each of these energy substrates to ATP generation is tightly regulated, and there is a significant degree of plasticity and interdependence between energy substrates utilized. Under normal physiological conditions, fatty acids and carbohydrates (i.e. glucose and lactate) represent the primary metabolic fuels that sustain cardiac function, and upwards of 95% of ATP production is attributable to mitochondrial oxidative phosphorylation. In the normal adult heart, fatty acid β-oxidation accounts for 60–80% of ATP production [1,3–5], with the remainder being primarily accounted for by carbohydrate (glucose and lactate) oxidation, and the oxidation of ketone bodies.

Various cardiac pathological states can cause perturbations of the tightly regulated pathways of myocardial energy substrate metabolism, and these perturbations can contribute to the progression of myocardial injury. Ischemic heart disease(s) (including, but not limited to angina and myocardial infarction) occur when coronary blood flow is inadequate. As the heart extracts 70–80% of the molecular oxygen (O_2) per unit of blood delivered [6,7], myocardial ischemia occurs when O_2 availability is not sufficient to meet the O_2 requirements of the heart. The consequences of myocardial ischemia are dependent on the nature and severity of the ischemic episode, and the elapsed time to the subsequent re-establishment of coronary flow

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(i.e. reperfusion). The consequences of ischemic heart disease can include alterations in cardiac structure, deficits in cardiac mechanical function, and perturbations in energy substrate metabolism.

In Western society there has been a marked improvement in the number of patients surviving the deleterious consequences of myocardial ischemia, which has been attributed predominantly to improved therapies (i.e. evidence based pharmacological therapy, thrombolysis/thrombolytic therapy, and refinements in revascularization) and to a decreased prevalence of cardiovascular risk factors (e.g. hypertension, hypercholesterolemia, and smoking) [8,9]. However, with these improvements in survival there has been a concomitant increase in the prevalence of heart failure. Heart failure is a complex clinical syndrome, the etiology of which generally stems from pre-existing ischemic heart/coronary artery disease, or it is of non-ischemic and/or idiopathic origin [10,11]. Heart failure is characterized by the progressive inability of the heart to fill with, and eject adequate amounts of blood to meet the needs of the body [12,13]. Heart failure has emerged as the leading cause of morbidity and mortality in developed countries [14]. In addition to being accompanied by characteristic neuro-hormonal alterations including activation of the renin–angiotensin–aldosterone system (RAAS) and activation of the sympathetic nervous system [15,16]; heart failure is also accompanied by distinct alterations in energy substrate metabolism.

Classically, the treatment of ischemic heart disease and heart failure has focused on the use of pharmacological agents that alter systemic and/or cardiac hemodynamics. As knowledge of the mechanisms regulating cardiac energy substrate metabolism increases, and as alterations in energy substrate metabolism attend the above cardiac pathophysiologies, the modulation and optimization of energy substrate metabolism represents a novel and promising area for therapeutic intervention in ischemic heart disease and heart failure. The aim of this review is to present: i) an overview of cardiac energy substrate metabolism, ii) the metabolic phenotype of the ischemic/ischemic–reperfused heart, iii) the metabolic phenotype of the failing heart, and iv) the mechanistic rationale for the use of pharmacological agents that modify energy metabolism to limit the deleterious consequences of ischemic heart disease and heart failure.

2. Cardiac energy substrate metabolism

In the aerobic setting greater than 90% of the ATP produced in the heart is derived from mitochondrial oxidative phosphorylation [10,11]. Reducing equivalents (protons and electrons) are transferred from various energy substrates to the mitochondria by the reduced forms of flavin adenine dinucleotide ($FADH_2$) and nicotinamide adenine dinucleotide (NADH), generated by dehydrogenase reactions occurring in the fatty acid β-oxidation pathway, the tricarboxylic acid (TCA) cycle, and during the oxidative disposal of pyruvate (i.e. glucose oxidation). The extents to which the various metabolic pathways contribute to myocardial ATP production are dependent on energetic demand, which itself is determined by chronotropic and inotropic state, preload, and the systemic vascular resistance against which the heart must eject blood [10].

2.1. Fatty acid utilization

In the cytosolic compartment, free fatty acids (FFAs) require activation prior to further metabolism. FFAs are activated via esterification to CoA, which generates a fatty acyl-CoA moiety through an ATP dependent process catalyzed by a family of fatty acyl-CoA synthase (FACS) enzymes. In the cytosol, acyl-CoA molecules are bound to acyl-CoA binding protein (ACBP), and can have a number of different metabolic fates including use for phospholipid and triacylglycerol synthesis, signal transduction, or mitochondrial fatty acid β-oxidation [10]. The inner mitochondrial membrane is impermeable to fatty acyl-CoA molecules, and the mitochondrial uptake of fatty acyl-CoAs is thus mediated by a complex of proteins utilizing carnitine as a shuttle mechanism [17]. Carnitine palmitoyl-transferase I (CPTI) is localized to the outer mitochondrial membrane and converts fatty acyl-CoA molecules to their respective fatty acylcarnitine moieties [18,19], which are subsequently shuttled into the mitochondrial matrix space by carnitine translocase, and reconverted back to a fatty acyl-CoA moiety by carnitine palmitoyl-transferase II (CPTII), which is localized to the inner leaflet of the inner mitochondrial membrane [20–22]. In the mitochondrial matrix, fatty acyl-CoA (saturated acyl-chain) molecules are progressively dismembered through the process of fatty acid β-oxidation by the sequential action of the enzymes acyl-CoA dehydrogenase, enoyl-CoA hydratase, 3-L-hydroxyacyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase. Polyunsaturated and monounsaturated fatty acids (e.g. oleate) require auxiliary enzymes including 2,4-dienoyl-CoA reductase and enoyl-CoA isomerase which facilitate the generation of a *trans* double-bond [23], a prerequisite for fatty acid β-oxidation by the four major enzymes described. Fatty acid β-oxidation sequentially shortens fatty acyl-CoA molecules by 2 carbon units through the liberation of acetyl-CoA (which is further metabolized in the TCA cycle), while also generating reducing equivalents (NADH and $FADH_2$) which act as electron donors for the electron transport chain and the process of oxidative phosphorylation.

Important factors regulating the rate of fatty acid β-oxidation are the level of circulating FFA in the plasma and the intracellular level of malonyl-CoA [24,25]. The concentration of FFA in the plasma is dependent on both prandial and hormonal state. Circulating FFA concentrations increase with fasting, while decreasing in the post-prandial state due in part to the anabolic and anti-lipolytic effects of insulin [26–28]. An increase in catecholamine discharge (e.g. during ischemic or surgical stress) also increases the circulating FFA concentration by increasing lipolysis. One of the consequences of increased FFA delivery to the heart is an increase in the rate of fatty acid β-oxidation. In addition to being regulated by the availability of circulating FFA, the activities of the enzymes of mitochondrial fatty acid β-oxidation also influence the overall rates of fatty acid utilization [11,29]. The acyl-CoA dehydrogenase and 3-hydroxyacyl-CoA dehydrogenase enzymes are both sensitive to the ratios of $FAD/FADH_2$ and NAD^+/NADH in the mitochondrial matrix, and the enzyme 3-ketoacyl-CoA thiolase is sensitive to the mitochondrial acetyl-CoA/CoA ratio.

Malonyl-CoA is an endogenous regulator of fatty acid β-oxidation [30,31]. The intracellular levels of malonyl-CoA are determined by energy demand and its rates of synthesis and degradation. Malonyl-CoA is synthesized from cytosolic acetyl-CoA via acetyl-CoA carboxylase (ACC), while being degraded via malonyl-CoA decarboxylase (MCD) [30,31]. The activity of ACC is under phosphorylation control by 5′-AMP activated protein kinase (AMPK), a kinase that modifies the activity of a number of metabolic enzymes involved in regulating both fatty acid and glucose metabolism [32–35]. In addition, AMPK is also implicated in upregulating various energy producing processes [36–40], and as such is central in the regulation of energy substrate metabolism. Mitochondrial acetyl-CoA, via the formation of acetylcarnitine can be transported into the cytosol, and acetylcarnitine can subsequently be reconverted back to acetyl-CoA by the action of cytosolic carnitine acetyl transferase [41]. In addition, citrate also influences malonyl-CoA levels. A proportion of citrate that escapes oxidation in the mitochondrial matrix by the TCA cycle, can utilize the mitochondrial tricarboxylate transporter to translocate to the cytosolic compartment, where it can allosterically activate ACC [42] or serve as a contributor to cytosolic acetyl-CoA via the ATP citrate lyase reaction [43,44]. Malonyl-CoA regulates fatty acid β-oxidation by inhibiting the activity of CPTI [45–47], the rate limiting enzyme of mitochondrial fatty acid uptake, thereby controlling the entry of fatty acids into the mitochondria for subsequent oxidation.

2.2. Glucose utilization

The stimulation of myocardial glucose transport involves an increase in the recruitment of GLUT1 as well as GLUT4 from intracellular

compartments to the sarcolemma [48]. Once glucose enters the cytosolic compartment, the enzymes hexokinase I and/or hexokinase II phosphorylate glucose, thereby generating glucose-6-phosphate (G-6-P). Interestingly, during fetal life, GLUT1 [49,50] and hexokinase (HK) I [49] are the predominant glucose transporter and HK isoforms present in the heart, but following birth, cardiac GLUT1/HK I expression decreases, while GLUT4 expression and HK II expression increases [49,50]. As the failing heart reverts to a fetal metabolic phenotype, the expression of distinct GLUT and hexokinase isoforms may be involved in determining metabolic profile (see Section 5.1). G-6-P is effectively trapped in the cell as a substrate for either of two metabolic fates, storage in the form of glycogen, or catabolism by glycolysis.

Glycolysis is the biochemical process that, in the cytosol, converts glucose to lactate or pyruvate under anaerobic or aerobic conditions, respectively. There is a net production of 2 moles (mol) ATP/1 mol of exogenous glucose that passes through glycolysis. The enzyme 6-phosphofructo-1-kinase (PFK-1) is the first regulatory site that commits glucose to catabolism by glycolysis [51]. Flux through PFK-1 is allosterically inhibited by ATP, citrate, and protons [51]. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), the first enzyme of the ATP generating stage of glycolysis, is involved in the oxidation and phosphorylation of glyceraldehyde phosphate coupled to the production of NADH from NAD^+ [52]. To ensure that flux through GAPDH is not limited NADH must be continually reoxidized to NAD^+, which can be accomplished by one of two routes. In the absence of O_2, NADH is reoxidized by the enzyme lactate dehydrogenase (LDH), which converts pyruvate to lactate, whereas in the presence of O_2, NADH is reoxidized by the malate/aspartate shuttle and mitochondrial electron transport chain.

Pyruvate oxidation (i.e. glucose oxidation) requires pyruvate transport into the mitochondria via a monocarboxylate carrier [53]. In the mitochondrial matrix, pyruvate can be carboxylated; however, in the heart the majority of pyruvate undergoes oxidative decarboxylation by the pyruvate dehydrogenase (PDH) complex yielding acetyl-CoA [54–56]. The PDH complex consists of PDH itself, PDH kinase (PDK), and PDH phosphatase, and is regulated both by its substrates and products (i.e. substrate/product ratios), and by covalent modification [57–59]. Generally only a small fraction (~20%) of PDH is in the active form, and this proportion is increased in response to an increase in glycolytic flux (and hence an increased generation of pyruvate), or in response to increased cardiac workload or catecholamine stimulation. PDH is also sensitive to inhibition by its products, as an increase in either the ratio of NADH/NAD^+ and/or acetyl-CoA/CoA decreases the rate of pyruvate decarboxylation [57,60,61]. With respect to covalent modification, PDH phosphatase dephosphorylates and activates PDH, whereas PDH kinase (PDK), in response to acetyl-CoA and NADH phosphorylates and inhibits PDH, thereby restricting the oxidation of carbon units derived from glycolysis [57,60].

2.3. Energy substrate competition — the glucose/fatty acid cycle

The reciprocal relationship between fatty acids and glucose for oxidative metabolism (glucose/fatty acid cycle) was originally described by Randle et al. in 1963 [28]. The molecular mechanisms underlying the glucose/fatty acid cycle are apparent at various stages of the pathways involved in the catabolism of each substrate (Fig. 1). Acetyl-CoA and NADH produced from fatty acid β-oxidation inhibit the PDH complex. Citrate derived from fatty acid ß-oxidation-derived acetyl-CoA can inhibit PFK-1 which in turn can lead, albeit to a lesser extent, to an inhibition of hexokinase by G-6-P [27]. As the inhibition of PDH is the most significant consequence of elevated rates of fatty acid β-oxidation, the effect of high fatty acid β-oxidation rates is an uncoupling between the rates of glycolysis and subsequent glucose oxidation (pyruvate oxidation). As pyruvate is a charged species, its transport across the inner mitochondrial membrane requires the co-transport of protons in a 1:1 stoichiometric manner [53,62], following which pyruvate is oxidized by the PDH complex. Therefore, when the rates of glycolysis are uncoupled from glucose oxidation protons produced from the hydrolysis of glycolytically derived ATP are not coupled to pyruvate co-transport across the inner mitochondrial membrane, and can thus produce intracellular acidosis [63,64]. The uncoupling of glucose metabolism, especially during periods of ischemia when blood flow is insufficient to remove metabolic by-products, can influence cardiac ionic homeostasis and cardiac efficiency (see Sections 3 and 4).

Conversely, increasing the contribution of glucose oxidation to the generation of acetyl-CoA can decrease fatty acid β-oxidation via feedback inhibition of 3-ketoacyl-CoA thiolase, while NADH derived from glucose oxidation can decrease fatty acid β-oxidation via feedback inhibition of both acyl-CoA dehydrogenase and 3-hydroxyacyl-CoA dehydrogenase. Furthermore, an increase in glucose-derived acetyl-CoA, via the actions of the enzymes carnitine acetyltranferase [11,65] and ACC can increase the synthesis of cytosolic malonyl-CoA, a negative regulator of mitochondrial fatty acid uptake and oxidation. Also, increasing glucose oxidation improves the coupling of glucose metabolism, and hence decreases proton production. The reciprocal inhibition of fatty acid β-oxidation, and decreases in proton production attributable to increased glucose oxidation have the potential to influence cardiac efficiency.

3. Cardiac energy substrate metabolism and cardiac efficiency

Cardiac mechanical efficiency, defined originally by Bing et al. [66] refers to the relationship between mechanical energy generated (i.e. cardiac work) and energy consumed (i.e. oxygen consumption — MVO_2) by the ventricle during contraction, and is expressed as the work/MVO_2 ratio. As cardiac muscle, under aerobic conditions meets the majority (>95%) of its energetic requirements via the oxidation of fatty acids and carbohydrates [11], MVO_2 provides a sufficient measure of energy input for contraction. Also, as the rates of cardiac energy metabolism are tightly coupled to energy demand, there is a good correlation between MVO_2 and cardiac work [67,68]. Recent reports point to the importance of metabolism in determining cardiac efficiency [69]. Cardiac contraction is driven by the hydrolysis of ATP, the vast majority of which is formed from mitochondrial oxidative phosphorylation (>95% under aerobic conditions), as such, cardiac efficiency is influenced by the efficiency of ATP generation and the efficiency of converting the chemical energy of ATP hydrolysis into mechanical work. These factors in turn are influenced by the intrinsic nature of the energy substrate (fatty acid vs carbohydrate) oxidized. Altering cardiac efficiency by targeting the balance between fatty acid β-oxidation and glucose oxidation may represent a suitable therapeutic intervention in the treatment of both ischemic heart disease (see Sections 4 and 6) and heart failure (see Sections 5 and 6).

3.1. Phosphorous/oxygen ratios and the efficiency of ATP generation

Phosphorous/oxygen (P/O) ratios of oxidative phosphorylation define the number of molecules of ATP produced per atom of oxygen reduced by the mitochondrial electron transport chain [70], and differ depending on the type of energy substrate utilized for the generation of mitochondrial NADH and $FADH_2$. Comparing palmitate and glucose as energy substrates, the complete oxidation of one palmitate molecule generates 105 molecules of ATP, while the complete oxidation of one molecule of glucose generates 31 molecules of ATP. Although fatty acid β-oxidation clearly generates the larger amount ATP, it comes at the expense of a greater oxygen requirement than carbohydrate oxidation. The P/O ratio of palmitate is less than that of glucose, making palmitate a less efficient substrate for ATP synthesis. Therefore, at any given level of cardiac work, an increased dependence on fatty acids relative to carbohydrates as an oxidative fuel

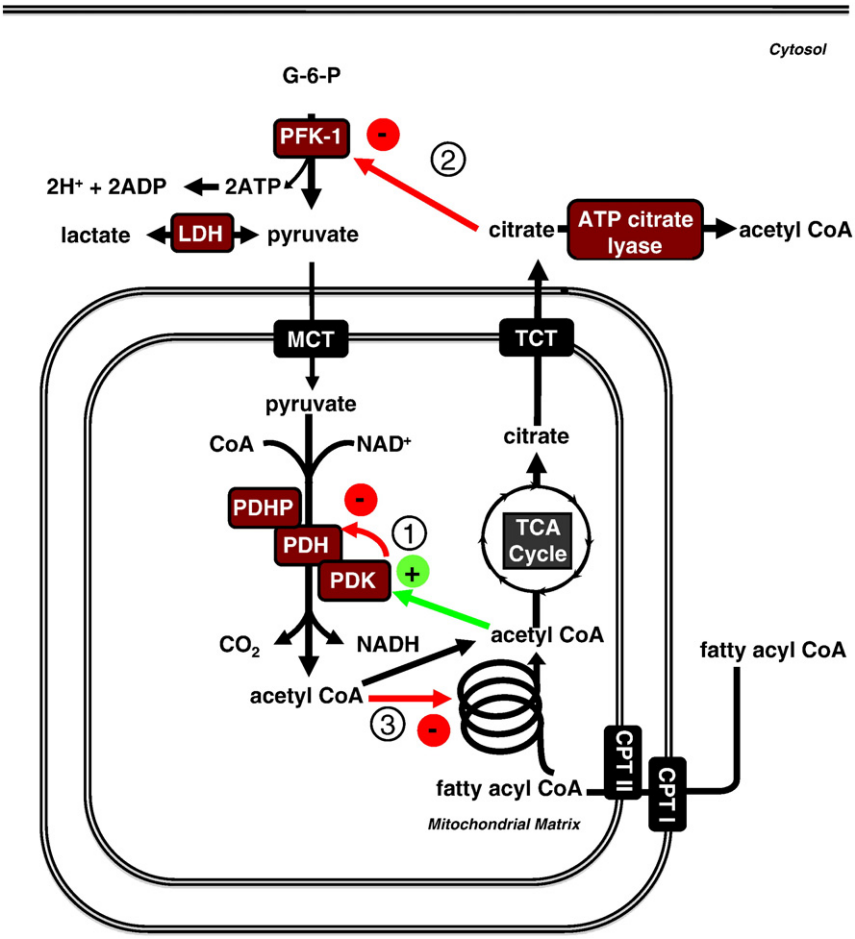

Fig. 1. The glucose/fatty acid cycle. The glucose/fatty acid cycle describes the reciprocal relationship between fatty acid and glucose metabolism. Acetyl-CoA and the reduced form of nicotinamide adenine dinucleotide (NADH) produced from fatty acid β-oxidation can inhibit the pyruvate dehydrogenase (PDH) complex (1). Citrate derived from fatty acid β-oxidation-derived acetyl-CoA inhibits phosphofructokinase-1 (PFK-1), the rate determining step of glycolysis, which in turn can lead to an inhibition of hexokinase by glucose-6-phosphate (G-6-P) (2). Increasing the contribution of glucose oxidation to the generation of acetyl-CoA decreases fatty acid β-oxidation via feedback inhibition of 3-ketoacyl-CoA thiolase, in addition, NADH derived from glucose oxidation can decrease fatty acid β-oxidation via feedback inhibition of both the acyl-CoA dehydrogenase and 3-hydroxyacyl-CoA dehydrogenase reactions (3).

(which occurs during reperfusion following ischemia and in the early stages of heart failure) decreases cardiac efficiency. Cardiac efficiency only differs by a theoretical value of 10–13% when calculated on the basis of P/O ratios using exclusively palmitate or glucose as an oxidative fuel. However, reported differences are much larger, ranging from 25–40%, suggesting there are additional mechanisms by which the balance between fatty acid and carbohydrate oxidation influences cardiac efficiency.

3.2. Uncoupling proteins and cardiac efficiency

The synthesis of ATP via oxidative phosphorylation is dependent on the electrochemical proton gradient across the inner mitochondrial membrane, generated by the translocation of protons from the mitochondrial matrix to the intermembrane space by complexes I, III, and IV of the electron transport chain [70,71]. The subsequent movement of protons down the electrochemical gradient via the F_1/F_0 ATPase into the mitochondrial matrix provides the chemical energy required for ATP synthesis [71]. Uncoupling proteins (UCP1–UCP5) are a family of mitochondrial proteins that provide an alternate route for the movement of protons from the intermembrane space to the matrix that is uncoupled from ATP synthesis. Ventricular muscle primarily expresses UCP2 and UCP3, with recent reports implicating UCP3 in regulating fatty acid-induced uncoupling of oxidative phosphorylation [72,73]. These effects may contribute to the mechanisms responsible for the decreased efficiency of ATP generation with the use of fatty acids as an oxidative fuel. Interestingly, recent reports demonstrate a positive correlation between circulating FFA concentrations and the expression of both UCP2 and UCP3 in the failing heart [74], which may uncouple oxidative phosphorylation, thereby decreasing ATP synthesis and cardiac efficiency [75]. Increased cardiac fatty acid utilization in hearts from insulin-resistant/diabetic *ob/ob* and *db/db* mice is associated with increased MVO_2, and uncoupled mitochondrial respiration, effects that also decrease rates of ATP synthesis and cardiac efficiency [76–80]. The decrease in cardiac efficiency may be attributed to increased MVO_2 [76,78,79], decreased LV work [77,80] or a combination of both [77,80].

3.3. Futile cycling of fatty acid intermediates and cardiac efficiency

Although equivocal [81], an additional role of UCP3 is the export of fatty acid anions from the mitochondrial matrix, an effect which may contribute to the futile cycling of fatty acid intermediates, and hence ATP wasting in the presence of elevated fatty acid utilization. When the supply of fatty acyl-CoA to the mitochondria exceeds the capacity to utilize it via fatty acid β-oxidation [82] mitochondrial thioesterase enzymes (MTEs) can hydrolyze surplus fatty acyl-CoA yielding free CoA and fatty acid anions. As mitochondria cannot regenerate the fatty acyl-CoA moiety, the fatty acid anion is proposed to be exported

to the cytosolic compartment by the transport function of UCPs. This function of UCPs, in conjunction with mitochondrial thioesterases may protect against the accumulation of potentially deleterious fatty acid anions in the matrix, as well as preventing the depletion of matrix CoA [83]. However, this would be associated with a significant ATP wasting effect as the exported fatty acid anion requires activation/esterification prior to further metabolism. This requires the action of acyl-CoA synthase. This reaction consumes the equivalent of 2 ATP molecules as it releases AMP and PPi, and as such does not generate ADP (which can be salvaged to ATP by the adenylate kinase reaction).

Fatty acids can also cycle between their acyl-CoA moieties and the intracellular triacylglycerol pool [84,85]. The cycling between acyl-CoA species and triacylglycerol has been reported to account for approximately 30% of total cellular energy expenditure [86]. This is attributed to the requirement for ATP-dependent re-esterification of fatty acids liberated from the triacylglycerol pool prior to subsequent β-oxidation or for the subsequent re-incorporation into the triacylglycerol pool. Futile cycling via these routes contributes to decreased cardiac efficiency by decreasing the efficiency of converting ATP hydrolysis to contractile work when fatty acid utilization is increased. Although direct evidence for this type of futile cycling is lacking in the ischemic and failing heart, it nonetheless may provide a possible mechanism contributing to the observed deficits in cardiac efficiency.

4. Metabolic phenotype of ischemic and ischemic–reperfused hearts

Various forms of ischemic heart disease including angina pectoris, acute myocardial infarction, and heart failure profoundly affect cardiac energy substrate metabolism and function. In the ischemic myocardium there is a rapid loss of contractile force, a depletion of high energy phosphates, and disturbances of ionic homeostasis. Alterations in the availability of oxygen and circulating energy substrates, as well as alterations in the mechanisms regulating substrate metabolism contribute to the metabolic phenotype(s) during both ischemia and reperfusion with respect to the utilization of carbohydrates and fatty acids, which in turn impact cardiac efficiency and function.

4.1. Anaerobic glycolysis

Glycolysis becomes a very important source of energy during ischemia due to its ability to generate ATP in the absence of O_2 (Fig. 2). Although glycolytic ATP production may be sufficient to maintain/correct ionic homeostasis during mild to moderate ischemia, the hydrolysis of glycolytically-derived ATP uncoupled from subsequent pyruvate oxidation leads to the increased generation of lactate and protons. During severe/total ischemia, due to a lack of blood flow, the metabolic by-products of glycolysis are not removed, and flux through the pathway is eventually inhibited due to the accumulation of protons (intracellular acidosis) at the level PFK-1 and GAPDH [52,87]. These effects can further aggravate disturbances in ionic homeostasis.

Decreased ATP production during ischemia compromises the function of various ATPase enzymes involved in regulating ionic homeostasis. Impaired activity of the Na^+/K^+ ATPase, which extrudes 3 Na^+ ions in exchange for 2 K^+ ions [88] leads to intracellular Na^+ overload. Impaired activity of the sarcolemmal and sarcoplasmic Ca^{2+} ATPases which are responsible for the extrusion and reuptake of Ca^{2+} into the sarcoplasmic reticulum, respectively, leads to intracellular Ca^{2+} overload [89]. Intracellular acidosis also impairs myofilament responsiveness to Ca^{2+}, thereby contributing to the loss of contractile force during ischemia, and can contribute to impaired recovery of post-ischemic mechanical function. The accelerated rates of glycolysis characteristic of the ischemic period can resolve during reperfusion [90–92], and still remain uncoupled from glucose oxidation.

4.2. Fatty acid β-oxidation and carbohydrate oxidation

Factors including prandial state and catecholamine discharge affect the concentration of circulating FFA. Plasma FFA concentration is elevated in the fasting state, while it is decreased in the post-prandial state due to an insulin-induced inhibition of adipose tissue lipolysis [27,28]. Ischemic stress increases catecholamine discharge, and plasma norepinephrine (NE) levels. Depending on the severity of the ischemic insult, catecholamine levels can remain elevated for prolonged periods of up to 24 h [93]. Catecholamines stimulate adipose tissue lipolysis, decrease pancreatic insulin release, and decrease peripheral insulin sensitivity [94–96]. Ischemic stress is also accompanied by elevated plasma levels of hydrocortisone, which can blunt insulin sensitivity [97]. Taken together these alterations have permissive effects on adipose tissue lipolysis leading to increased plasma concentrations of FFA and increased delivery of FFA to the myocardium. The increased delivery of FFA to the myocardium can alter fatty acid utilization during both ischemia, and reperfusion following ischemia.

The prerequisite for oxygen in the process of oxidative phosphorylation results in a rapid decline in ATP production from fatty acid β-oxidation and glucose oxidation that is proportional to the degree of ischemia. Nonetheless, fatty acid β-oxidation remains the predominant process for residual oxidative metabolism [98–101]. The decrease in glucose oxidation during ischemia necessitates a rapid acceleration in the conversion of pyruvate to lactate via LDH in order to regenerate NAD^+ under anaerobic conditions, which is required to maintain glycolytic flux through GAPDH. In the case of total ischemia, NADH, and $FADH_2$ can accumulate [102], and inhibit the acyl-CoA dehydrogenase and 3-hydroxyacyl-CoA dehydrogenase enzyme reactions of fatty acid β-oxidation [1]. Also, acylcarnitine species can accumulate in both the mitochondrial matrix and cytosolic compartments, while acyl-CoA species can accumulate primarily in the mitochondrial matrix [103]. The accumulation of acylcarnitine and acyl-CoA species can promote the disruption of mitochondrial cristae, and the formation of amorphous intramitochondrial densities. These changes in mitochondrial ultrastructure may ultimately disrupt mitochondrial function [104].

In the post-ischemic period, the rates of fatty acid β-oxidation rapidly recover to near pre-ischemic values, whereas the rates of glucose oxidation, cardiac efficiency, and mechanical function remain depressed [92,105,106]. Furthermore, as reperfusion rapidly normalizes extracellular pH, it generates a large trans-sarcolemmal proton gradient that increases Na^+/H^+ exchange and exacerbates intracellular Na^+ overload incurred during ischemia. In turn, Na^+ overload promotes reverse mode activation of the Na^+/Ca^{2+} exchanger, which extrudes 3 Na^+ in exchange for 1 Ca^{2+}, thereby contributing to intracellular Ca^{2+} overload during reperfusion [89,107]. These disturbances in ionic homeostasis during ischemia and in the post-ischemic period during reperfusion contribute to deficits in both cardiac function and cardiac efficiency, both of which can be improved by therapies that optimize myocardial energy substrate metabolism.

5. Metabolic phenotype of the failing heart

Heart failure is characterized by alterations in cardiac hemodynamics and reflex neuro-endocrine activation (sympathetic nervous system, renin–angiotensin aldosterone system) secondary to depressed contractile function. Experimentally, heart failure can be induced in response to volume-overload, pressure-overload, rapid ventricular pacing, genetic alterations (transgenic animals), or myocardial infarction [108,109]. As such, multiple cardiovascular diseases including ischemic heart disease(s), hypertension, as well as cardiomyopathies of genetic origin can progress, ultimately to heart failure. As heart failure itself progresses to its advanced stages,

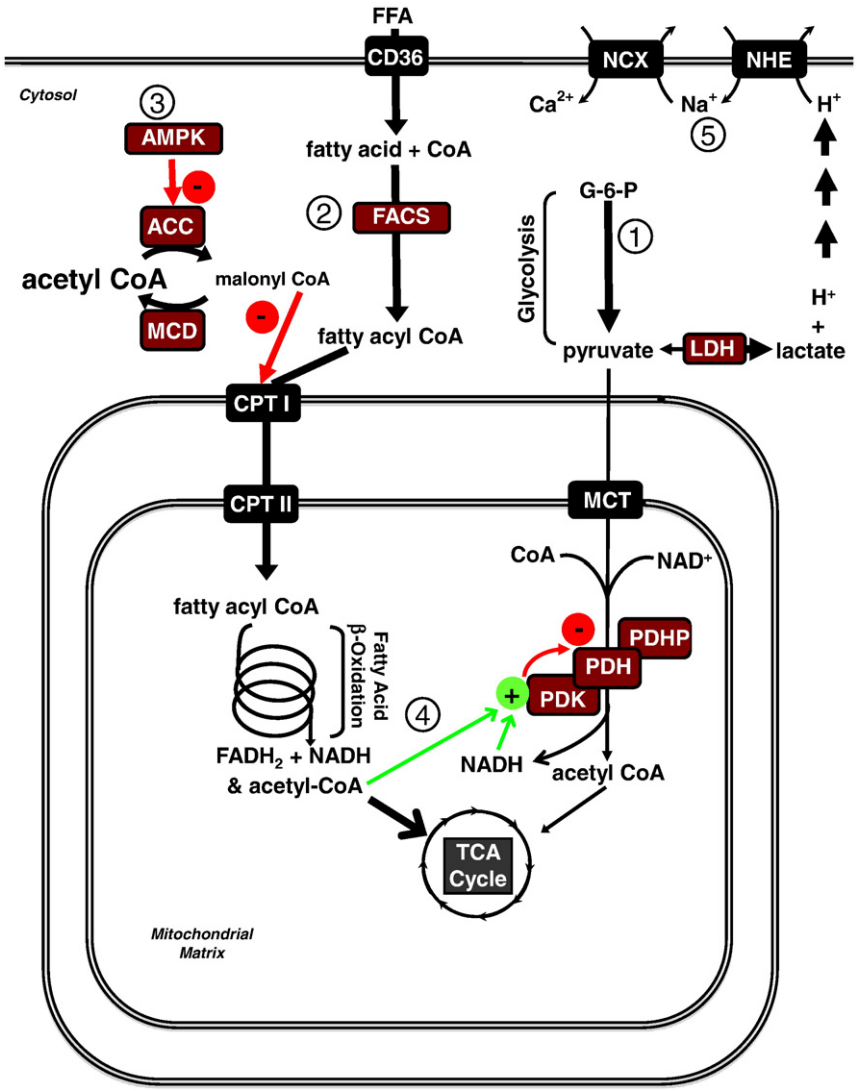

Fig. 2. Alterations in myocardial energy substrate metabolism in ischemia/reperfusion. During ischemia, glycolysis becomes an important source of ATP production in response to a decrease in the supply of oxygen, or in the absence of oxygen (1). Fatty acids dominate as the substrate for residual oxidative metabolism due to increased plasma levels of fatty acids (2) as well as the activation of 5′-adenosine monophosphate activated protein kinase (AMPK) which decreases the production of malonyl-CoA, the endogenous inhibitor of carnitine palmitoyl-transferase-I (CPTI) (3). During reperfusion, glycolytic rates remain high, while fatty acid oxidation dominates over glucose oxidation as the main source of oxidative metabolism. The dominance of fatty acid oxidation during reperfusion inhibits glucose oxidation (4). The uncoupling of glycolysis from glucose oxidation leads to increased proton production, which ultimately leads to myocardial acidosis and calcium overload (5).

myocardial ATP content decreases in the range of 30–40% relative to ATP content in the normal heart, [110–113], in addition there are decreases in creatine Cr and phosphocreatine PCr content (see for review [2,114,115]). Furthermore, the PCr/ATP ratio is decreased in heart failure and correlates well with New York Heart Association (NYHA) functional class [116]. Defects in the rates of oxygen consumption and mitochondrial electron transport chain activity, which impact oxidative phosphorylation, and hence ATP generation accompany the advanced stages of heart failure (see for review [2,11]). Such deficits in energy generating processes and energetic intermediates suggest that alterations in energy substrate metabolism are important biochemical hallmarks of, and contributors to the pathogenesis and progression of heart failure.

5.1. Reversion to the fetal metabolic profile

Pathological hypertrophy is maladaptive, and progresses to heart failure. Pathological cardiac hypertrophy results in a number of cellular changes, including alterations in contractile proteins [117–120]. Furthermore, it is now apparent that pathological hypertrophy in the mature heart is accompanied by a reversion to a fetal pattern of energy substrate metabolism [118,119,121]. Specifically, glycolysis increases in pressure-overload cardiac hypertrophy [122–124], while fatty acid oxidation decreases [122,125,126]. These effects are accompanied by parallel changes in the activity and/or expression of enzymes involved in these metabolic pathways [120,127,128].

Members of the peroxisome proliferator activated receptor (PPAR) superfamily are involved in regulating fatty acid metabolism. There are three distinct isoforms of PPAR (PPARα, PPARβ/δ, and PPARγ), and each has distinct cardiovascular effects. PPARα is predominantly expressed in the heart, muscle, and liver, PPARβ is expressed in a more ubiquitous manner, with high levels in both cardiac and skeletal muscle, while PPARγ is predominantly expressed in adipose tissue and exists at lower levels in cardiac and skeletal muscle [129]. The peroxisome proliferator activated receptor (PPAR) isoforms PPARα and PPARβ/δ may influence the fetal metabolic phenotype observed in the presence of pathological cardiac hypertrophy. Genetic deletion of PPARα is associated with cardiac hypertrophy, and decreased rates of fatty acid β-oxidation [130]. PPARα and peroxisome proliferator activated receptor γ coactivator (PGC)-1α levels are also decreased in

the hypertrophied heart [131]. In contrast, the upregulation of cardiac myocyte PPARα suppresses hypertrophy by attenuating increases in protein synthesis [132,133], and also prevents the downregulation of the expression of the muscle isoforms of CPTI [133]. However, the precise role of the PPARα in cardiac hypertrophy/failure has not been completely resolved. Specifically, although cardiac-specific overexpression of PPARα increases myocardial fatty acid β-oxidation [134], it is also associated with cardiac hypertrophy [134,135]. Cardiac-specific ablation of PPARβ/δ is also accompanied by decreased myocardial fatty acid β-oxidation [136]. Interestingly, cardiac specific overexpression of PPARβ/δ does not increase myocardial fatty acid oxidation; however, it does increase glucose oxidation, an effect associated with the increased expression of cardiac GLUT4 [137]. This effect may be related to the ability of PPARβ/δ to improve insulin sensitivity [138,139]. The lack of change in fatty acid β-oxidation in response to PPARβ/δ overexpression may be attributable to the reciprocal relationship between fatty acid and carbohydrate oxidation described by the glucose/fatty acid cycle.

In the hypertrophied heart there is an increase in glycolysis [122,140], which is accompanied by increased expression levels of GLUT1 [141], and increased activity of the glycolytic enzyme enolase [142]. Despite the acceleration of glycolysis, glucose and lactate oxidation rates remain low [122]. Recent reports indicate that this may be due to a compensatory increase in pyruvate carboxylation via malic enzyme and pyruvate carboxylase required to replenish the TCA cycle by anaplerosis in the setting of cardiac hypertrophy [56]. Therefore, there is a reversion to the fetal metabolic profile, where ATP production is more dependent on glycolysis and less so on fatty acid β-oxidation and glucose oxidation in the setting of pathological hypertrophy, which itself can progress to heart failure.

5.2. Myocardial fatty acid and glucose utilization in heart failure

Alterations in energy substrate metabolism accompanying heart failure are extremely complex, in part due to the heterogeneous nature of heart failure itself. Specifically, the metabolic phenotype of the failing heart appears to be at least in part dependent on the stage/severity of the syndrome; however, the metabolic alterations are not clear cut. In ventricular homogenates obtained from hearts subjected to pressure overload with preserved ejection fraction, the rates of fatty acid β-oxidation are similar to homogenates obtained from normal hearts, whereas the rates of glycolysis are accelerated [143]. Furthermore, fatty acid β-oxidation rates are also similar in ventricular homogenates obtained from hearts subjected to myocardial infarction and subsequent heart failure at a time point when there is a downregulation in genes encoding enzymes involved in fatty acid oxidation including acyl-CoA synthase and CPTI [144]. These findings are also extrapolated to the whole heart, where fatty acid β-oxidation does not differ in acute heart failure secondary to aortic banding in rats [145], or in the canine microembolization model, where glucose uptake and oxidation are also preserved relative to the normal heart [146].

Previous studies indicate that despite decreased fatty acid uptake (likely owing to decreased regional coronary blood flow), cardiac fatty acid β-oxidation is normal in patients with asymptomatic hypertrophic cardiomyopathy [147]. Additionally, a previous report examining primarily NYHA functional class III patients indicates that fatty acid utilization is increased secondary to enhanced lipolysis [148]. The increased fatty acid utilization is also accompanied by elevated plasma lactate concentrations, indicative of fatty acid-induced impairments in whole-body carbohydrate oxidation [148]. Interestingly, in clinically stable NYHA functional class II and III patients cardiac fatty acid uptake [149,150] and fatty acid β-oxidation [149] were greater than that observed in healthy controls, while glucose uptake [150] and oxidation were lower [149]. These alterations in cardiac fatty acid and glucose utilization in NYHA functional class II–III patients may negatively impact cardiac efficiency, and may thus represent a viable therapeutic target to modulate the balance between fatty acid and glucose utilization in heart failure.

Recent studies indicate that experimental models of severe end-stage heart failure are accompanied by a depression in overall oxidative metabolism. Twenty weeks following pressure overload-induced heart failure, secondary to transverse aortic constriction in rats, there is a decrease in mitochondrial state 3 respiration, as well as a decrease in both fatty acid (i.e. oleate) and glucose oxidation [151,152]. Interestingly, in these studies the ratio between fatty acid β-oxidation and glucose oxidation is not altered. This contrasts with observations in the canine model of severe heart failure induced by rapid ventricular pacing. In this model, severe heart failure is accompanied by decreased rates of fatty β-oxidation, and increased rates of glucose oxidation [153–155]. The increase in glucose oxidation appears to be paradoxical, as protein expression of PDH is decreased, while that of its negative regulator, PDK4 is increased [153]. The decrease in fatty acid β-oxidation in severe heart failure was accompanied by decreased expression of retinoid X receptor (PPAR binding partner), and decreased expression of medium chain acyl-CoA dehydrogenase (MCAD) [154]. The metabolic phenotype observed in pacing-induced heart failure is reversible, as the rates of fatty acid β-oxidation increase, while the rates of glucose oxidation decrease during a recovery phase following discontinuation of rapid-ventricular pacing [155].

The findings of decreased fatty acid β-oxidation in experimental models of severe heart failure are also transferable to the clinical setting, as the rates of both fatty acid uptake and oxidation are decreased in patients with dilated cardiomyopathy (ejection fraction ~32%), while the rates of glucose uptake are increased [156]. Furthermore, in such patients, there is an inability to increase fatty acid and glucose uptake in response to pacing stress, which contributes to mechanical inefficiency [156]. Such defects in fatty acid and glucose uptake may suggest a considerable degree of ineffective substrate utilization under basal conditions. Energy substrate supply is also a critical determinant of cardiac performance and efficiency in patients with heart failure. Marked and acute reductions in circulating fatty acid levels in response to acipimox (an inhibitor of lipolysis) treatment are accompanied by large reductions in fatty acid uptake, and decreased cardiac efficiency, although fractional fatty acid β-oxidation remains unchanged [157]. These results indicate that FFAs are an important energy substrate in the failing heart, and are in line with the previous suggestion that, "the heart functions best when it oxidizes two substrates simultaneously [158]." Alternatively, these findings also lend support to previous observations demonstrating that pharmacologically targeting the balance between fatty acid β-oxidation and glucose oxidation as opposed to markedly limiting FFA availability may be a viable therapeutic strategy to improve cardiac efficiency in these patients (see Section 6).

5.3. Elevated sympathetic nervous activity, elevated plasma fatty acids, and insulin resistance in heart failure

Activation of cardiac β-adrenoceptors represents one of the most powerful physiological inputs to acutely enhance cardiac performance. Thus, in an attempt to preserve cardiac output, heart failure (in particular, systolic heart failure) is often accompanied by hyperactivity of the sympathetic neuro-humoral axis (see for review [15,16]). For the purposes of this section, we will only deal with the neuronal limb of the sympathetic nervous system and its contribution to elevated plasma fatty acid levels during heart failure. However, it should be noted that the participation of the humoral limb and the renin–angiotensin–aldosterone system is equally important [159,160]. Elevated sympathetic nervous system activity in heart failure is associated with increased circulating NE levels, plasma spillover of NE from activated sympathetic nerve fibers, and increased central sympathetic outflow [161]. In untreated heart failure patients,

excess NE spillover may approximate circulating NE levels observed in healthy individuals following intense exercise [162].

β-adrenoceptor antagonists, which are a mainstay therapy in the treatment of a number of cardiovascular diseases ranging from angina to heart failure, act via oxygen-sparing mechanisms linked to a reduction in cardiac energy demand. In the setting of heart failure, treatment with β-adrenoceptor antagonists is associated with improved left ventricular performance, reversal of adverse left ventricular remodeling, reduced hospitalization, and ultimately, enhanced patient survival [16]. Mechanisms involved in the protective benefits of β-adrenoceptor antagonists in the treatment of heart failure include: 1) inhibition of the cardiotoxic effects of excessive catecholamine discharge, 2) upregulation of β_1-adrenoceptors, 3) improvement in subendocardial coronary flow, 4) attenuation of pro-apoptotic, growth promoting, and vasoconstrictive pathways, 5) restoration of reflex control, and 6) improved myocardial performance due to reduced cardiac energy demand and oxygen consumption.

Reductions in cardiac energy demand and oxygen consumption have important implications with regards to fatty acid metabolism in the failing heart, as the consequences of increased sympathetic nervous system activity in heart failure are important contributing factors towards its metabolic phenotype. Excess circulating NE levels will result in elevated rates of adipose tissue lipolysis, which will subsequently increase the delivery of circulating FFAs to the heart. Presumably, by reducing neuro-humoral hyperactivity, β-adrenoceptor antagonists can reduce catecholamine-induced lipolysis and therefore decrease circulating plasma FFA levels. Indeed, β-adrenoceptor antagonists decrease the mobilization of FFAs from adipose tissue [163], and therefore lower plasma FFA concentrations [164,165]. Furthermore, sympathetic hyperactivity, reflected by increased circulating levels of catecholamines and FFAs is reduced by the β-adrenoceptor antagonist propranolol during the course of myocardial infarction [93]. 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 [166,167], while increasing LV function in the absence of increased oxygen utilization [168,169]. Second, activation of β_1- and β_2-adrenoceptors in the heart results in chronotropic and inotropic effects, which increase the demand on the heart and subsequent oxygen consumption. Interestingly, β^1-adrenoceptors are downregulated and NE uptake decreased in the failing heart [170,171]. Nonetheless, as heart failure patients have elevations of sympathetic nervous system activity, the availability of circulating FFAs is increased. Interestingly, increases in cardiac energy demand brought about by increased cardiac work are associated with elevated fatty acid oxidation rates [172]. Thus, one would anticipate that this effect in combination with the enhanced lipolytic effect accompanying sympathetic nervous system activation may negatively affect the balance between fatty acid β-oxidation and glucose oxidation, and so lead to impairments in cardiac efficiency.

Sympathetic nervous system hyperactivity and excess catecholamine release also impair insulin sensitivity, which contributes to increased circulating FFA levels as well as the development of whole body insulin resistance [173]. Indeed, clinical studies demonstrate that decreasing plasma FFA levels attenuates insulin resistance [174]. Furthermore, insulin resistance is an important contributor to, and is highly prevalent in the pathogenesis of heart failure. Interestingly, higher proinsulin levels (a surrogate marker for insulin resistance) were observed in patients who subsequently developed heart failure versus control patients 20 years before the actual diagnosis of heart failure itself [175]. Indeed, whole body insulin resistance (which largely reflects changes in skeletal muscle insulin-sensitivity) precedes the development of heart failure in humans [176,177]. Whether the myocardium itself is insulin resistant is often a question of debate [178]. However, studies using ^{18}F-fluoro-2-deoxyglucose (FDG) positron emission tomography have shown that heart failure patients with type 2 diabetes do exhibit myocardial insulin resistance, as indicated by a significant reduction in myocardial FDG uptake [179]. Furthermore, the canine model of rapid ventricular pacing-induced heart failure is associated with a robust myocardial insulin resistance, as seen by a complete absence of insulin-stimulated myocardial glucose uptake following hyperinsulinemic–euglycemic clamp [180,181].

An important area of concern when interpreting metabolic changes in heart failure patients with accompanying insulin resistance/type 2 diabetes is the fact that the metabolic phenotypes of each disease state are extremely complex. In both animal and human studies, myocardial metabolism in insulin resistance is associated with enhanced fatty acid oxidation rates, reduced glucose oxidation rates, and depending on the severity of insulin resistance, either reduced or unchanged glycolytic rates [78,79,182–189]. In contrast, as the severity of heart failure increases, fatty acid oxidation rates decrease while glycolytic rates increase, with no real change in glucose oxidation rates as the heart adapts a more fetal metabolic phenotype [10,11]. The fact that there is ongoing debate with regards to the metabolic changes that take place in isolation in both the failing heart and the diabetic heart is undoubtedly compounded by the fact that the patient population often harbors both of these diseases. Thus, it will be extremely important for future studies to try and determine the relative contribution each disease state has on myocardial metabolism, in order to determine the best metabolic therapeutic approach.

6. Optimizing energy substrate metabolism — a novel therapeutic intervention in the ischemic and failing heart

Myocardial ischemia is accompanied by elevated plasma FFA concentrations and a subsequent increase in the supply of FFAs to heart. Interestingly, in the setting of ischemia, and under conditions of increased FFA supply, cardiac fatty acid β-oxidation dominates as the source of residual oxidative metabolism [100,190,191], while glucose oxidation is depressed [100,191]. Furthermore, during reperfusion fatty acid β-oxidation also rapidly recovers, leading to an inhibition of pyruvate dehydrogenase and an increased production of lactate and protons [63,64,92,105]. Heart failure is also characterized by complex alterations in oxidative energy substrate metabolism that are amenable to pharmacological interventions. Optimizing energy substrate metabolism by inhibiting fatty acid β-oxidation, while increasing glucose oxidation (Fig. 3) may provide a means to increase the efficiency of ATP production and utilization in order to restore cardiac efficiency and thus improve function in both the ischemic/reperfused heart and the failing heart. However, it is important to note that in the failing heart, the actual severity of heart failure may determine whether inhibition of fatty acid oxidation is a viable therapeutic approach, as in the most severe stages of heart failure mitochondrial function is severely diminished. As such, there may be negative consequences associated with reducing oxidative capacity even further [11].

6.1. Targeting the availability of circulating FFAs

Therapeutically decreasing circulating FFA concentration may represent a viable strategy to decrease the delivery of FFA to the myocardium, and hence decrease cardiac fatty acid β-oxidation in the post-ischemic period as well as in heart failure. Interestingly, in heart failure, a marked reduction/depletion of plasma FFA can acutely and transiently impair cardiac efficiency, suggesting the importance of fatty acids as an oxidative substrate in this setting [157]. Therefore, the degree to which circulating FFA concentration is decreased may be an important factor determining the subsequent effects on cardiac efficiency and function.

6.1.1. Glucose–insulin–potassium therapy

Glucose–insulin–potassium (GIK) therapy has been shown to increase the rates of glycolysis and also decrease circulating

concentrations of FFA [192,193]. The shift toward glucose utilization decreases infarct size [192] and improves post-ischemic cardiac function [194]. A number of studies also demonstrate that GIK therapy is beneficial when administered at reperfusion [192,195,196]. However, it should be noted that the effects of insulin itself are influenced by the level of circulating FFA supplied to the myocardium [197]. A disproportionate stimulation of glycolysis relative to glucose oxidation can uncouple the two processes, contribute to intracellular acidosis [92], and may attenuate the cardioprotective effects of insulin [197]. Interestingly, there are reports demonstrating a lack of infarct size reduction in response to GIK treatment [198]. The Diabetic Patients with Acute Myocardial Infarction (DIGAMI) study [199] demonstrates a significant long term reduction in mortality in diabetic patients treated with insulin following myocardial infarction. Other studies including the Estudios Cardiologicos Latinoamerica Collaborative Group Study (ECLA) with thrombolysis and percutaneous coronary intervention [195], and the Glucose–Insulin–Potassium Study demonstrate a reduction in mortality, although the benefit is limited to patients without heart failure [196]. However, a Polish study failed to show GIK-induced improvements in survival or the clinical course of acute myocardial infarction [200]. A more recent Dutch GIK study also showed a potentially higher mortality in the GIK group [201]. Thus, there is still no clear consensus as to whether GIK therapy is beneficial in the treatment of myocardial ischemia, exemplified by acute myocardial infarction.

6.1.2. β-adrenoceptor antagonists

β-adrenoceptor antagonists are used in the setting of ischemic heart disease and heart failure in part due to their negative inotropic and chronotropic effects that decrease cardiac workload and elicit oxygen sparing. β-adrenoceptor antagonists decrease catecholamine-induced lipolysis and therefore decrease plasma FFA availability and extraction. As such, propranolol has been shown to reduce the increased sympathetic activity during the course of myocardial infarction [93] while carvedilol has been shown to reduce myocardial FFA uptake by 57% in patients with heart failure [166,167]. These effects may be attributed, at least in part to the ability of β-adrenoceptor antagonists to inhibit CPTI activity [202], and promote glucose oxidation [203], and hence decrease the oxygen costs of ATP generation. Interestingly, neither mean myocardial uptake of ^{18}F-FDG nor the rate of glucose utilization increased significantly. Metoprolol, another β-adrenoceptor antagonist, shows no effect on circulating FFA [204]. Nonetheless, β-adrenoceptor antagonists improve left ventricular function independent of alterations in cardiac oxygen consumption [168,169], effects indicative of improved cardiac efficiency.

6.1.3. Peroxisome proliferator activated receptor ligands

Fibrates, which are selective PPARα agonists, decrease circulating FFAs, primarily by increasing hepatic expression of fatty acid oxidation enzymes [205], as well as increasing FACS expression [206]. The decrease in circulating FFA concentration and decreased cardiac FFA extraction may decrease myocardial fatty acid β-oxidation, and suggest the possible utility of these compounds in the treatment of ischemic heart disease. These effects are evident in models of diet-induced obesity and insulin resistance, as mice subjected to diet-induced obesity and treatment with fenofibrate exhibit a significant increase in hepatic fatty acid oxidation rates [184]. Furthermore, this increase in extra-cardiac fatty acid oxidation is associated with a reduction in circulating triacylglycerol concentrations, likely contributing to the observed reduction in myocardial fatty acid oxidation rates and subsequent increase in glucose oxidation rates, which ultimately resulted in enhanced recovery of post-ischemic function. In addition, fibrates can also reduce infarct size in animal models [207] and improve the recovery of post-ischemic function [208].

PPARβ/δ is involved in regulating the expression of genes involved in cardiac fatty acid metabolism including FACS, the muscle isoforms of CPTI, long chain acyl-CoA dehydrogenase, and medium-chain acyl-CoA dehydrogenase [136,209,210]. Furthermore, the PPARβ/δ-mediated increases in the expression of genes involved in fatty acid metabolism are accompanied by the expected increases in the rates of myocardial fatty acid utilization, particularly increased rates of fatty acid β-oxidation [209,211,212]. In cardiac myocytes, PPARβ/δ activating ligands also prevent the downregulation of: i) genes involved in fatty acid metabolism and ii) fatty acid β-oxidation in response to hypertrophic stimuli [211,212]. Furthermore, PPARβ/δ is also involved in regulating the expression of genes involved in myocardial glucose metabolism, including GLUT4, and phosphofructokinase, and cardiac specific overexpression of PPARβ/δ increases the rates of myocardial glucose oxidation [137]. These effects may be beneficial in limiting the attenuation of the rates of oxidative metabolism in the setting of heart failure; however, this remains to be investigated.

PPARγ is the target of the thiazolidinedione (TZD) class of antidiabetic drugs. TZDs promote lipid sequestration in adipose tissue, thereby decreasing ectopic deposition and storage of excess lipid. Experimental studies have demonstrated a decrease in plasma triacylglycerol and FFA concentrations with TZD administration. Myocardial glucose [213] and lactate [214] uptake and oxidation [215] have also been shown to increase with TZD treatment. This increase in glucose utilization, at the expense of fatty acid utilization may potentially improve cardiac efficiency. Indeed, TZDs do have favorable effects on post-ischemic cardiac function [213–216]. These findings are also extrapolated to experimental models of diabetes, as *db/db* mice treated for 5 weeks with rosiglitazone have decreased circulating FFA concentrations, which reduce myocardial fatty acid oxidation rates, and subsequently increase glucose oxidation rates, as well as cardiac efficiency. These beneficial effects improve the recovery of post-ischemic cardiac function [217]. In contrast, cardiac specific overexpression of PPARγ is associated with the development of cardiomyopathy and disrupted mitochondrial architecture [218]. Furthermore clinical trials investigating the use of TZDs in diabetic heart failure patients have raised concerns about its safety. Particularly, increased fluid retention and vascular permeability have been implicated in aggravating heart failure in diabetic patients [219]. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) Study demonstrated an increased incidence of heart failure in patients treated with pioglitazone [220]. Recent meta-analysis of the risk of myocardial infarction and cardiovascular mortality suggests that rosiglitazone therapy causes an increased risk of myocardial infarction, although no increase in cardiovascular or all cause mortality was observed [221,222]. However, the post-hoc analysis of the BARI 2D trial indicated that there was no increase in myocardial infarction or risk of death from rosiglitazone (Bach et al. ADA late breaking clinical studies session, 2010). Thus it remains to be determined whether PPARγ agonists are detrimental in heart failure and/or ischemic heart disease until the results of Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial are completed.

6.2. Targeting mitochondrial fatty acid uptake

As the rate-limiting enzyme mediating mitochondrial fatty acid uptake, CPTI is an attractive target for inhibiting myocardial fatty acid β-oxidation. A number of CPTI inhibitors have been developed, including etomoxir and perhexiline, both of which have been demonstrated to have anti-ischemic/oxygen-sparing effects as well as having beneficial effects in the treatment of heart failure.

6.2.1. Etomoxir

Etomoxir is an irreversible inhibitor of CPTI [223]. The compound has been shown to improve myocardial function, concomitant with an

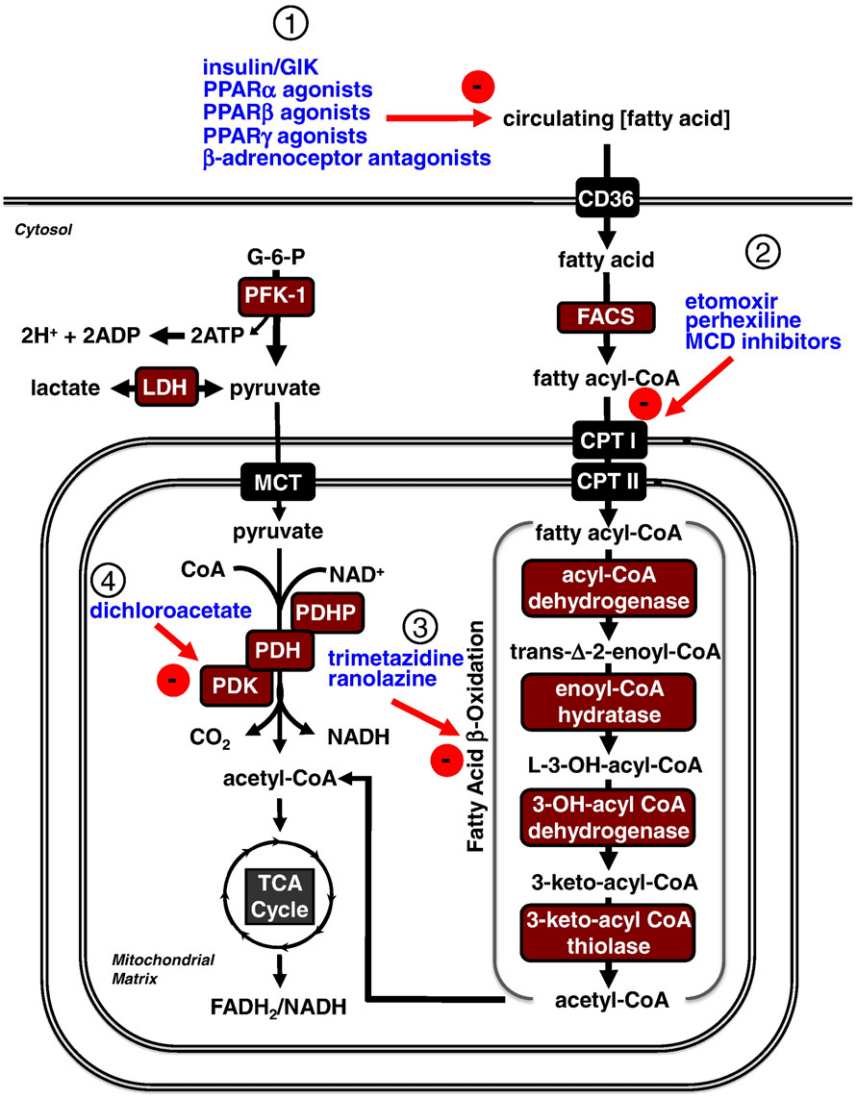

Fig. 3. Targeting fatty acid and glucose oxidation as a therapeutic intervention in ischemic and ischemic/reperfused hearts, and the failing heart. Fatty acid oxidation can be targeted at different levels for treatment of both ischemic heart disease and heart failure. Circulating fatty acids can be decreased with the use of glucose–insulin–potassium (GIK), peroxisome proliferator activated receptor (PPAR) agonists and β-adrenoceptor antagonists (1). The mitochondrial uptake of long chain acyl-CoAs can be reduced with the use of carnitine palmitoyl tranferase-I (CPTI) and malonyl-CoA decarboxylase (MCD) inhibitors (2). Partial fatty acid oxidation inhibitors can inhibit the rates of myocardial fatty acid oxidation (4). Glucose oxidation can be increased with the use compounds that increase pyruvate dehydrogenase (PDH) complex activity by inhibiting PDK4 (5).

increase in glucose oxidation after global ischemia in the rat heart [224–226] as well as in hearts from diabetic rats [227,228]. Thus etomoxir possesses anti-ischemic effects and may potentially be effective in the treatment of diabetic cardiomyopathy. Etomoxir treatment has also been shown to improve ventricular function in rat hearts subjected to pressure overload [229], which can progress to heart failure. Furthermore, etomoxir is suggested to be effective in treating heart failure by improving the rate of sarcoplasmic reticulum calcium uptake in the setting of cardiac hypertrophy [230]. However, results of clinical trials with etomoxir remain inconclusive. The first open-label trial with etomoxir (80 mg daily for 3 months) showed an improvement in LV ejection fraction, cardiac output at peak exercise, and clinical status in patients with NYHA class II heart failure [231]. However, a more recent double-blind multi-centered clinical trial was prematurely terminated due to unacceptably high liver transaminase levels in 4 etomoxir-treated patients [232].

6.2.2. Perhexiline

Perhexiline was originally utilized as an anti-anginal agent in the 1970's. However, cases of hepatic failure and neuropathy have led to the decline of its use. The toxicity is related to phospholipid accumulation, a direct consequence of CPTI inhibition. However, it has recently been shown that toxicity can be dramatically reduced by titrating the plasma concentration of perhexiline to between 150 to 600 ng/mL, which inhibits the cardiac but not hepatic isoform of CPTI. When added to maximum anti-anginal therapy, with plasma-guided dose titration, perhexiline decreases the frequency of angina attacks, while increasing exercise capacity [233]. Perhexiline has also been demonstrated to be effective in chronic heart failure improving left ventricular ejection fraction and VO_2 max [234], as well as improving overall cardiac energetics [235]. These beneficial effects suggest that perhexiline-induced alterations in fatty acid utilization, at the level of mitochondrial fatty acid uptake are therapeutically relevant in the treatment of both ischemic heart disease(s) and heart failure.

6.2.3. Malonyl-CoA decarboxylase inhibitors

Inhibitors of MCD activity increase malonyl-CoA content in both mouse and rat hearts [236,237]. The inhibition of MCD has been shown to cause an increase in glucose oxidation and insulin sensitivity in rodents [32]. Administration of specific MCD inhibitors to working

hearts results in a decrease in fatty acid β-oxidation and an increase in glucose oxidation, improved cardiac efficiency, and an increase in the recovery of post-ischemic function [236,238–240]. The ability to alter the balance between fatty acid β-oxidation and glucose oxidation also persists in the swine model of demand-induced ischemia [238,239]. Thus pharmacologically increasing malonyl-CoA content, to subsequently decrease mitochondrial fatty acid uptake and fatty acid β-oxidation has salutary effects in the setting of ischemic heart disease (s). It remains to be determined whether these effects are also transferable to heart failure.

6.3. Targeting mitochondrial fatty acid β-oxidation

Another approach to inhibit mitochondrial fatty acid oxidation is to directly inhibit the enzymes of fatty acid β-oxidation. A number of fatty acid β-oxidation inhibitors have been developed and have been proven effective against ischemic heart disease and heart failure.

6.3.1. Trimetazidine

Trimetazidine is a partial fatty acid β-oxidation inhibitor that competitively inhibits long chain 3-ketoacyl-CoA thiolase (KAT) [241,242]. The inhibition of fatty acid β-oxidation is accompanied by an increase in glucose oxidation. This would be beneficial in ischemia as increased glucose oxidation can decrease proton production arising from the uncoupling of glycolysis from glucose oxidation. Interestingly, trimetazidine has also been shown to lack inhibitory effects on 3-KAT in rat hearts [243]. In the setting of pressure-overload cardiac hypertrophy (where the rate of fatty acid β-oxidation is already decreased), trimetazidine has been shown to be cardioprotective independent of alterations in fatty acid β-oxidation, but rather, via reductions in glycolysis which subsequently decrease proton production [244]. The decrease in proton production improves the coupling between glycolysis and glucose oxidation, an effect demonstrated to attenuate acidosis, improve cardiac efficiency and cardiac function [92,245].

Results from clinical studies have confirmed the effectiveness of trimetazidine as an anti-ischemic agent. Treatment of angina with trimetazidine has been shown to increase the time to 1-mm ST segment depression, while decreasing weekly nitrate consumption [246,247]. Trimetazidine has been shown to have comparable effectiveness as propranolol in treating stable angina [248]. Combination therapy with standard anti-anginal therapy has also been shown to reduce the number of symptomatic episodes of angina and improve time to ischemia-related ECG changes on exercise testing [249]. Trimetazidine is also effective in treating heart failure. Trimetazidine normalizes the PCr/ATP ratio in patients with ischemic cardiomyopathy [250]. The addition of the drug to treatment regimens improves NYHA functional class, LV end-diastolic volume and ejection fraction in patients with heart failure and ischemic cardiomyopathy [250,251]. Trimetazidine is also effective in the treatment of non-ischemic/idiopathic heart failure. In patients with idiopathic dilated cardiomyopathy, trimetazidine has been shown to improve LV ejection fraction. This improvement coincides with a decrease in myocardial fatty acid β-oxidation without changes in total myocardial oxidative rates, implying an increase in glucose utilization [252]. Interestingly, the improved ejection fraction is accompanied by a decrease in fatty acid oxidation by only 10% in the failing heart, suggesting that additional effects may partly be responsible for the observed benefit. Indeed, an increase in β1-receptor blockade with the use of trimetazidine has also been indicated, suggesting a synergistic effect with β-adrenoceptor antagonists [252].

6.3.2. Ranolazine

Ranolazine is a partial fatty acid β-oxidation inhibitor, which reciprocally increases glucose oxidation [253,254] and PDH activity [255,256]. The protective effects of ranolazine have been associated with the shift from fatty acid β-oxidation to glucose oxidation without a concomitant increase in glycolysis [254] or lactate release [255], indicative of improved coupling between glycolysis and glucose oxidation. Besides inhibiting fatty acid β-oxidation, ranolazine has also been shown to inhibit the electron transport chain in damaged and uncoupled mitochondria and is postulated to prevent ATP wasting attributable to futile cycling [257]. Ranolazine can also directly inhibit the late Na^+ current and prevent adverse increases in diastolic $[Ca^{2+}]_i$ attributable to Na^+-dependent Ca^{2+} overload and thus limit ischemic myocardial injury [258,259]. Recently, it has been proposed that the inhibition of the late Na^+ current is the mechanism responsible for the cardioprotective effects of ranolazine based on the apparent lower concentration ($\leq$10 μM) [260] required for Na^+ current inhibition versus that required for partial fatty acid oxidation inhibition (100 μM) [243], as well as the observation that inhibition of fatty acid β-oxidation by the fatty acid oxidation inhibitor CVT-4325 does not improve left ventricular function in ischemic rat hearts [261]. However, a number of studies have demonstrated improved cardiac function concomitant with increased glucose oxidation and decreased fatty acid oxidation at the therapeutic concentration of $\leq$10 μM [254,255]. Thus, it is possible that both late Na^+ current inhibition and partial inhibition of fatty acid β-oxidation contribute to the cardioprotective effects of ranolazine.

In experimental studies, ranolazine has been shown to attenuate myocardial stunning and reduce infarct size in rabbit hearts [262,263]. In a canine heart failure model, ranolazine can acutely increase cardiac ejection fraction, stroke volume and mechanical efficiency without increasing oxygen consumption [264,265], while 3 months of treatment prevents the progression of LV remodeling and contractile dysfunction [266]. Clinically, ranolazine has been approved in the United States for the treatment of chronic stable angina. Ranolazine monotherapy has been shown to increase exercise capacity and time to 1-mm ST segment depression [267,268], and to reduce the number of weekly angina attacks [269]. When added to standard anti-anginal therapy, ranolazine also confers additional protection [269,270]. Antiarrhythmic effects, attributed to the inhibition of late Na^+ current, have also been demonstrated clinically with the use of ranolazine in patients with non-ST-segment elevation acute coronary syndromes, showing decreased incidence of ventricular tachycardia, supraventricular tachycardia, and new onset atrial fibrillation [271]. The anti-ischemic effects and antiarrhythmic effects of ranolazine appear to occur at similar concentrations and may both contribute to its cardioprotective efficacy.

6.4. Targeting the pyruvate dehydrogenase complex and glucose oxidation

6.4.1. Pyruvate dehydrogenase kinase inhibitors

In both ischemic heart disease as well as heart failure, there are defects in oxidative fatty acid and glucose metabolism. The beneficial effects of both trimetazidine and ranolazine in the ischemic/reperfused heart and failing heart suggest that altering the balance between fatty acid and glucose oxidation, such that it favors glucose oxidation has salutary effects on cardiac function. Directly increasing myocardial glucose oxidation represents another approach to improve cardiac function. Dichloroacetate (DCA) stimulates the mitochondrial PDH complex via the inhibition of the activity of PDK. Improved coupling between glycolysis and glucose oxidation contributes to the mechanism(s) by which DCA exerts its cardioprotective effects [92,245]. Experimental studies show that DCA increases post-ischemic recovery of cardiac function in neonatal rabbit [272], rat [105] as well as swine hearts [273]. Furthermore, DCA increases glucose oxidation rates in hearts obtained from rats treated with streptozotocin (an experimental model of type 1 diabetes). The stimulation of glucose oxidation was associated with an improvement in LV developed pressure [274], however, the DCA-induced increase in

myocardial glucose oxidation did not enhance the recovery of post-ischemic function [275].

Clinical data on the use of DCA is scarce. In a small clinical study, where DCA was given to patients with coronary artery disease via intravenous infusion, improvements in LV stroke volume was observed in the absence of changes in heart rate, left ventricular end diastolic pressure or myocardial oxygen consumption [276]. Furthermore, a recent study indicates that treatment of Dahl salt-sensitive rats attenuates the transition from left ventricular hypertrophy to heart failure, beneficial effects associated with improved myocardial energetics [277]. A potential advantage with regards to the use of DCA as opposed to the use of insulin is the selective stimulation of glucose oxidation in the post-ischemic period [106,278–282], whereas insulin stimulates both glycolysis and glucose oxidation. As such, DCA improves the coupling between glycolysis and glucose oxidation thereby decreasing proton production, while insulin can uncouple the two processes leading to an increase in proton production during reperfusion. These effects may contribute to the controversial results of trial of GIK therapy [197].

In addition to DCA several other inhibitors of PDK activity have been developed. The novel PDK inhibitor SDZ048-619 increases PDH activity in cardiac muscle, skeletal muscle, liver, and kidney in the diabetic Zucker rat [283,284]. The compound AZD7545 (a selective PDK2 inhibitor) has been demonstrated to increase PDH activity in liver (where PDK2 is the predominant isoform) with lesser increases in cardiac and skeletal muscle [285]. Whether or not these compounds elicit alterations in cardiac glucose oxidation similar to those elicited by DCA remains to be characterized; nonetheless, these additional PDK inhibitors may be useful pharmacological tools to further validate the stimulation of glucose oxidation as a therapeutic target in the ischemic and failing heart.

6.5. Medium chain fatty acids

Medium chain fatty acids (MCFA) typically possess acyl-chain lengths of 6–12 carbons, are saturated, and have unique metabolic properties that differ from those of long chain FFAs [286]. Specifically, MCFAs do not require protein-mediated transport to cross the sarcolemmal or mitochondrial membranes. As such, MCFAs bypass CPTI and are activated in the mitochondrial matrix by the enzyme medium chain acyl-CoA synthetase. Owing to these metabolic properties, MCFAs appear to be preferentially directed towards fatty acid β-oxidation as opposed to incorporation into triacylglycerol. Such an effect may have the potential to limit the futile cycling of fatty acids through the triacylglycerol pool [86], and hence decrease wasteful ATP hydrolysis (see Section 3.3). Furthermore, MCFAs of odd chain lengths including 7, and 9 carbons generate the anaplerotic substrate, propionyl-CoA after 2 or 3 rounds of fatty acid β-oxidation, respectively. These effects may be of relevance in both the ischemic–reperfused heart as well as the failing heart.

Despite the ability to increase the myocardial contents of the TCA cycle intermediates citrate [287], malate [288], and fumarate [288] MCFAs do not improve the recovery of post-ischemic function [287,288]. Although the direct effects of MCFAs in the failing heart have not been examined, several studies have characterized their effects in the presence of pressure overload cardiac hypertrophy (i.e. in the spontaneously hypertensive rat model), which can progress to heart failure. Dietary supplementation with MCFAs corrects hyperinsulinemia, attenuates cardiac hypertrophy, prevents the rise in LV diastolic pressure, and limits decrements in contractile function [289–291]. With respect to energy substrate metabolism, MCFAs prevent decreases in the expression of MCAD, while attenuating increases in the expression of PFK-1 in the presence of cardiac hypertrophy [290]. These findings may suggest that MCFAs are capable of preventing the downregulation of oxidative metabolism and concomitant shift towards glycolysis in the hypertrophied heart. Interestingly, in the presence of cardiac hypertrophy, in response to adrenergic stress (which commonly accompanies heart failure), the contribution of exogenous long chain fatty acids (e.g. oleate) to energetic requirements decreases, and is not accompanied by a compensatory increase in carbohydrate oxidation, but rather enhanced lactate release [292], indicative of an uncoupling between glycolysis and glucose oxidation. Under these conditions, the MCFA octanoate is readily oxidized, and does not affect the oxidation of exogenous oleate [292]. Furthermore, octanoate increases tissue levels of TCA cycle intermediates, particularly isocitrate and malate [292], again suggesting that MCFAs are a readily oxidizable substrate that may surmount limited rates of oxidative metabolism in the hypertrophied heart. Whether MCFAs can elicit such alterations in oxidative metabolism and improve function in the failing heart remains to be addressed.

7. Limitations

7.1. Inhibition of fatty acid β-oxidation and lipotoxicity

A potential drawback associated with the inhibition of myocardial fatty acid oxidation during either ischemic heart disease or heart failure is that if fatty acids are not oxidized, they can be shuttled and stored as intra-myocardial triacylglycerol and other lipid intermediates including diacylglycerol and ceramide [10,293]. It has been proposed that the accumulation of lipid intermediates such as ceramide in the myocardium is directly toxic, and may lead to apoptotic cell death of cardiac myocytes, as well as myocardial fibrosis, LV chamber expansion, contractile dysfunction, and impaired diastolic filling, a collection of events often referred to as “cardiac lipotoxicity” [11,135,294–300]. Directly stimulating glucose oxidation with compounds such as DCA (as opposed to inhibiting fatty acid β-oxidation), may provide a means to circumvent cardiac lipotoxicity. However, increases in glucose oxidation can result in a secondary increase in malonyl-CoA content and subsequent inhibition of fatty acid oxidation via a Randle Cycle effect, thereby resulting in an accumulation of intra-myocardial triacylglycerol [301]. Although the general phenomenon of cardiac lipotoxicity has been observed in a number of genetic models in rodents, it remains poorly defined and continues to lack a clinically equivalent condition. Interestingly, several studies have now demonstrated dissociation between myocardial lipid accumulation and cardiac function, thereby suggesting that an increase in intra-myocardial triacylglycerol content does not necessarily equate to decreased contractile function [189,302].

7.2. Energy substrate metabolism in the isolated working heart preparation

The majority of studies assessing *in vitro* cardiac function and metabolism utilize the isolated working heart preparation. The isolated working heart preparation is an ideal experimental model for the simultaneous measurement of various indices of cardiac function and energy substrate metabolism. A major factor controlling flux through the pathways of fatty acid β-oxidation, glycolysis, glucose oxidation, and the tricarboxylic acid cycle is external work performed by the heart. The ability to perfuse the isolated heart at selected preload and afterload pressures, as well as with both glucose and fatty acids allows the characterization of cardiac substrate metabolism at relevant workloads as well as over a range of workloads, in either a physiological or pathological setting (e.g. failing heart). However, it must be noted that the majority of findings utilizing this experimental model, represent left ventricular function and left ventricular metabolism. As there is an absence of right ventricular load, the contribution(s) of right ventricular function and metabolism to overall cardiac function is (are) not apparent or assessed.

8. Conclusions

Cardiac fatty acid and glucose metabolism, specifically fatty acid β-oxidation and glucose oxidation, are highly regulated processes that meet the majority of myocardial energetic requirements. The balance between fatty acid β-oxidation and glucose oxidation is an important determinant of cardiac efficiency, and function. Cardiac ischemia, ischemia/reperfusion, and heart failure are characterized by complex alterations in fatty acid and glucose oxidation that ultimately have a negative impact on cardiac efficiency and function. Pharmacologically shifting the balance between fatty acid β-oxidation and glucose oxidation by targeting either i) the cellular uptake of energy substrates, ii) transcriptional regulators of energy substrate metabolism, iii) mitochondrial fatty acid uptake, iv) mitochondrial fatty acid β-oxidation, and v) glucose oxidation such that glucose oxidation is increased at the expense of fatty acid oxidation can improve the efficiency of ATP generation and hydrolysis. Such alterations in energy substrate metabolism can limit the deficits in cardiac efficiency and function that occur during cardiac ischemia and heart failure.

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