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Review

Targeting mitochondrial oxidative metabolism as an approach to treat heart failure ☆

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ABSTRACT

Heart failure is a major cause of morbidity and mortality in the world. Cardiac energy metabolism, specifically fatty acid and glucose metabolism, is altered in heart failure and has been implicated as a contributing factor in the impaired heart function observed in heart failure patients. There is emerging evidence demonstrating that correcting these changes in energy metabolism by modulating mitochondrial oxidative metabolism may be an effective treatment for heart failure. Promising strategies include the downregulation of fatty acid oxidation and an increased coupling of glycolysis to glucose oxidation. Carnitine palmitoyl transferase I (CPT1), fatty acid β-oxidation enzymes, and pyruvate dehydrogenase kinase (PDK) are examples of metabolic targets for the treatment of heart failure. While targeting mitochondrial oxidative metabolism is a promising strategy to treat heart failure, further studies are needed to confirm the potential beneficial effect of modulating these metabolic targets as an approach to treating heart failure. This article is part of a Special Issue entitled: Cardiomyocyte Biology: Cardiac Pathways of Differentiation, Metabolism and Contraction.

1. Introduction

Heart failure has become the most common cause of mortality in developed countries [1]. Heart failure most commonly is the result of either cardiac ischemia, cardiac hypertrophy, or is due to idiopathic origins [2,3]. Heart failure is characterized by a progressive decline in the ability of the heart to fill with and eject adequate amounts of blood to meet the requirements of the body [4,5]. The heart has a high energetic demand [6,7]. In pathological conditions such as heart failure and ischemic heart disease, the altered regulation of cardiac fatty acid and glucose metabolism is believed to contribute to impaired heart efficiency and function. There is evidence that therapeutically regulating cardiac metabolism by reducing fatty acid oxidation and/or increasing glucose oxidation can improve the function of the failing heart. This paper will review cardiac energy metabolism, metabolism of the failing heart, and the potential of metabolic targets for the treatment heart failure.

2. Cardiac metabolism

2.1. Glucose metabolism

The heart utilizes many substrates for energy metabolism, including glucose and fatty acids. Glucose uptake in cardiac muscle is regulated by the translocation of the glucose transporters GLUT1 and GLUT4 to the cell membrane [8]. The intracellular glucose is sequestered inside the cell by being phosphorylated to glucose-6-phosphate by either hexokinase I or II. In the adult cardiomyocyte the dominant isoforms are GLUT4 and hexokinase II while in the fetal heart the dominant isoforms are GLUT1 and hexokinase I [9,10]. Intracellular glucose can either be stored as glycogen or can enter the glycolytic pathway (Fig. 1). Phosphofructokinase 1 (PFK1) is the step in glycolysis at which glucose becomes completely committed to glycolysis [11]. During glycolysis, glucose is converted to pyruvate which is either oxidized (glucose oxidation) or converted to lactate (Fig. 1). When glycolysis is coupled to glucose oxidation, pyruvate enters the mitochondria via the mitochondrial pyruvate carrier (MPC), is converted to acetyl CoA by pyruvate dehydrogenase (PDH), and enters the tricarboxylic acid (TCA) cycle, eventually resulting in the production of 31 ATP per molecule of glucose metabolized [12–16]. When pyruvate does not enter glucose oxidation, it is converted to lactate by lactate dehydrogenase. One of the reasons this step is important is because it converts NADH back to NAD^+ so that it is available for glycolysis to continue. This occurs either under anaerobic conditions or when mitochondrial oxidation of the pyruvate is inhibited. If glucose is converted to 2 lactate molecules, then 2 ATP are produced from each glucose that passes through glycolysis.

Glucose oxidation is primarily regulated via the activity of PDH (Fig. 1). PDH is part of a complex that also contains PDH kinase (PDK) and PDH phosphatase (PDP) [17–19]. PDH is regulated by phosphorylation and by the levels of its products and substrates [17–19]. PDK inhibits PDH by phosphorylating it and PDP relieves this inhibition by dephosphorylating PDH [17,20]. The activity of PDK is increased by acetyl CoA and NADH [17,20]. The ratio of both NADH/NAD^+ and acetyl CoA/CoA regulates the activity of PDH, with higher values resulting in lower PDH activity [17,20,21]. In addition, PDH activity is increased by

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elevated pyruvate supply from glycolysis, as well as due to increased PDP activity (which can occur as a result of increased mitochondrial calcium concentrations due to catecholamine stimulation and increased cardiac workload) [22–24].

2.2. Fatty acid metabolism

Fatty acid β-oxidation is the process by which fatty acids are broken down to produce ATP. Fatty acids primarily cross the cell membrane via fatty acid protein transporters, which include fatty acid translocase (FAT/CD36), plasma membrane bound fatty acid binding protein ($FABP_{pm}$), and tissue specific fatty acid transport proteins (FATP) [25–28]. Fatty acyl CoA synthetase (FACS) then adds a CoA group to the fatty acid (Fig. 1). In a series of steps necessary for long chain CoAs to enter the mitochondria the long chain acyl CoA is converted to long chain acylcarnitine by carnitine palmitoyltransferase 1 (CPT1), following which carnitine acylcarnitine translocase (CAT) transports the fatty acid across the inner mitochondrial membrane, and CPT2 converts the acylcarnitine back to acyl CoA. The long chain acyl CoA can then enter fatty acid β-oxidation. One acetyl CoA is produced from each cycle through the pathway as well as NADH and $FADH_2$. The NADH and $FADH_2$ produced by both fatty acid β-oxidation and the TCA cycle utilization of the acetyl CoA are used by the electron transport chain to produce ATP.

2.3. Randle cycle

Fatty acid and glucose metabolism can regulate each other by a process called the glucose/fatty acid cycle, or the Randle Cycle [29]. The acetyl CoA and NADH produced by fatty acid oxidation can inhibit pyruvate dehydrogenase (Fig. 1) [23]. In addition, citrate inhibits PFK1 and by increasing glucose-6-phosphate levels indirectly inhibits hexokinase activity [30,31]. The acetyl CoA produced by PDH inhibits the fatty acid oxidation enzyme 3-ketoacyl CoA thiolase [23]. In addition, the NADH produced during glucose oxidation inhibits the fatty acid oxidation enzymes 3-hydroxyacyl CoA dehydrogenase and acyl CoA dehydrogenase [23]. Acetyl CoA can also be converted to malonyl CoA by acetyl CoA carboxylase (ACC), which inhibits fatty acid oxidation via malonyl CoA inhibition of CPT1 [3,11,31,32].

The inhibition of glucose oxidation due to high fatty acid oxidation rates is much more dramatic than the degree of glycolysis inhibition [2]. This increases the uncoupling of glycolysis from glucose oxidation, which can lead to intracellular acidosis due to the increased levels of lactate and protons produced [23,33]. Clearance of these protons can also result in the accumulation of calcium and sodium, requiring ATP expenditure to maintain these intracellular ion levels within a normal range [2].

2.4. Cardiac energy metabolism and efficiency

Cardiac efficiency is a measurement of the amount of oxygen required for a given amount of cardiac work. It can be defined as the amount of work produced by the heart per amount of O_2 consumed [23]. Since O_2 is required for mitochondrial oxidative metabolism, alterations in energy metabolism can affect cardiac efficiency. Compared to glucose, fatty acids are an inefficient energy substrate. The full oxidation of 1 glucose molecule requires 6 O_2 and produces 31 ATP. Palmitate oxidation requires 23 O_2 but only produces 105 ATP. However, the actual decrease in cardiac efficiency due to elevated fatty acid oxidation rates is actually much higher than expected due to calculated ATP/O_2 ratios (up to 30% instead of 10%), suggesting that other mechanisms are also involved in fatty acids reducing cardiac efficiency [2]. One of these mechanisms includes fatty acid inhibition of glucose oxidation, a more efficient metabolic pathway (see Randle Cycle section). Fatty acids also inhibit adenine nucleotide transferase (ANT) thereby inhibiting the transport of ATP from the mitochondrial matrix to the outside the mitochondria [2]. A third mechanism involves fatty acid activation of sarcolemmal calcium channels. More ATP has to be used to keep the cytosolic calcium levels at normal levels instead of being used for work [34]. Further, futile cycles may also contribute to fatty acid induced cardiac inefficiency. These futile cycles include uncoupling proteins (UCP) and the cycling of fatty acids between triacylglycerol and acyl CoA moieties (Fig. 2) [2]. UCP2 and UCP3 are believed to uncouple oxidative phosphorylation by dissipating the mitochondrial intermembrane proton gradient created by the electron transport chain [23,35]. In the failing heart, increases in circulating fatty acid levels correlate positively with increases in UCP2 and UCP3 protein expression [36]. In addition, UCP3 may reduce cardiac efficiency by transporting fatty acid anions out of the mitochondria [23,37].

Cycling of fatty acids between intracellular triacylglycerol stores and acyl CoA moieties is another cause of reduced cardiac efficiency (Fig. 2) [2]. The esterification of a fatty acid to a fatty acyl CoA requires two high

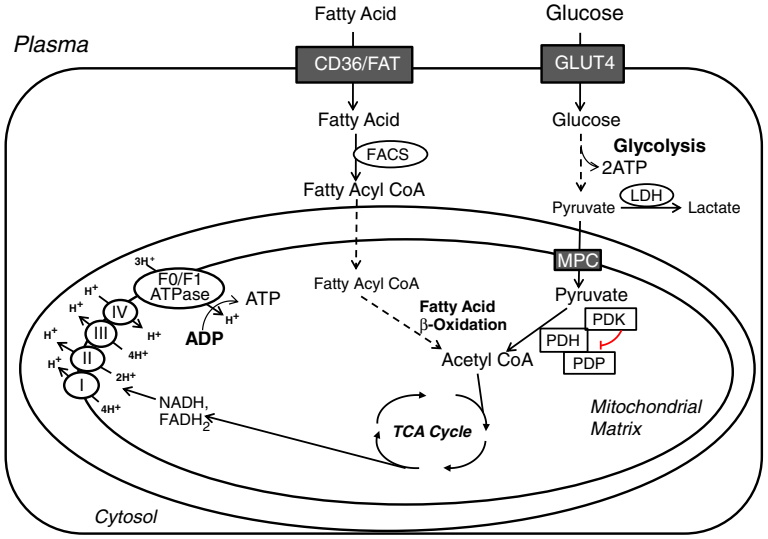

Fig. 1. Glucose and fatty acid metabolic pathways in the heart. In general, in the failing heart, mitochondrial oxidative metabolism decreases and glycolytic rates increase.

energy phosphates (ATP is converted to AMP). The fatty acyl CoA can either undergo fatty acid oxidation or be stored as triacylglycerol. To undergo fatty acid β-oxidation, the fatty acids must be liberated from triacylglycerol, a process which may contribute to the fatty acid induced cardiac inefficiency.

3. Cardiac energy metabolism in heart failure

The changes in cardiac metabolism during heart failure are complex and depend on the stage of heart failure [2]. The nature of these cardiac metabolic changes are further complicated by the fact that heart failure can have many causes including pressure overload, volume overload, myocardial infarction, and genetic alterations [38,39]. During the progression of heart failure, myocardial ATP content can decrease, and can drop to 60–70% of normal levels [2,40–43]. There is also a dramatic drop in phosphocreatine levels in the failing heart [42–44]. This is accompanied by a decrease in mitochondrial oxidative metabolism and a compensatory increase in glucose uptake and glycolysis [2,40–43,45–47]. This rise in glycolysis is an adaptation to the reduced oxidative metabolism. However, because this rise in glycolysis occurs independent of glucose oxidation, proton and lactate production also increases in the heart [2,48]. This increase in lactate and proton production has the potential to be detrimental to the heart. This uncoupling of glycolysis and glucose oxidation is even further exacerbated by a rise in circulating fatty acids that can occur in heart failure.

During heart failure cardiac energy metabolism appears to revert back toward a fetal metabolic phenotype. The decrease in fatty acid oxidation and rise in glycolysis observed in pressure overload hypertrophied hearts are accompanied by changes in expression and activity of metabolic enzymes involved in these pathways [49–56]. The expression of peroxisome proliferator activated receptor α (PPARα) and peroxisome proliferator activated receptor gamma coactivator 1 α (PGC-1α), enzymes that regulate mitochondrial biogenesis and fatty acid oxidation enzyme expression, are decreased in the hypertrophied heart [57]. In addition, GLUT1 protein expression and enolase activity, an enzyme in glycolysis, are increased in the hypertrophied heart [58,59].

The exact cardiac energy metabolic alterations are not completely consistent between models of heart failure and stages of heart failure. In hearts with preserved ejection fraction despite being subjected to pressure overload and infarcted hearts with heart failure fatty acid oxidation gene expression is reduced [46,60]. In addition, in heart failure caused by aortic banding fatty acid oxidation rates are reduced [61]. In severe end stage heart failure caused by aortic banding an overall depression of oxidative metabolism occurs [62,63]. In contrast, in severe heart failure caused by rapid ventricular pacing fatty acid β-oxidation rates are reduced and glucose oxidation rates are elevated [47,64,65]. It has also been reported that fatty acid uptake and oxidation is reduced and glucose uptake is increased in human hearts with dilated cardiomyopathy [66].

4. Treating heart failure by targeting mitochondrial oxidative metabolism

A considerable amount of emerging experimental and clinical data has shown that targeting cardiac energy metabolism can be beneficial in treating heart failure. The strategy of decreasing fatty acid

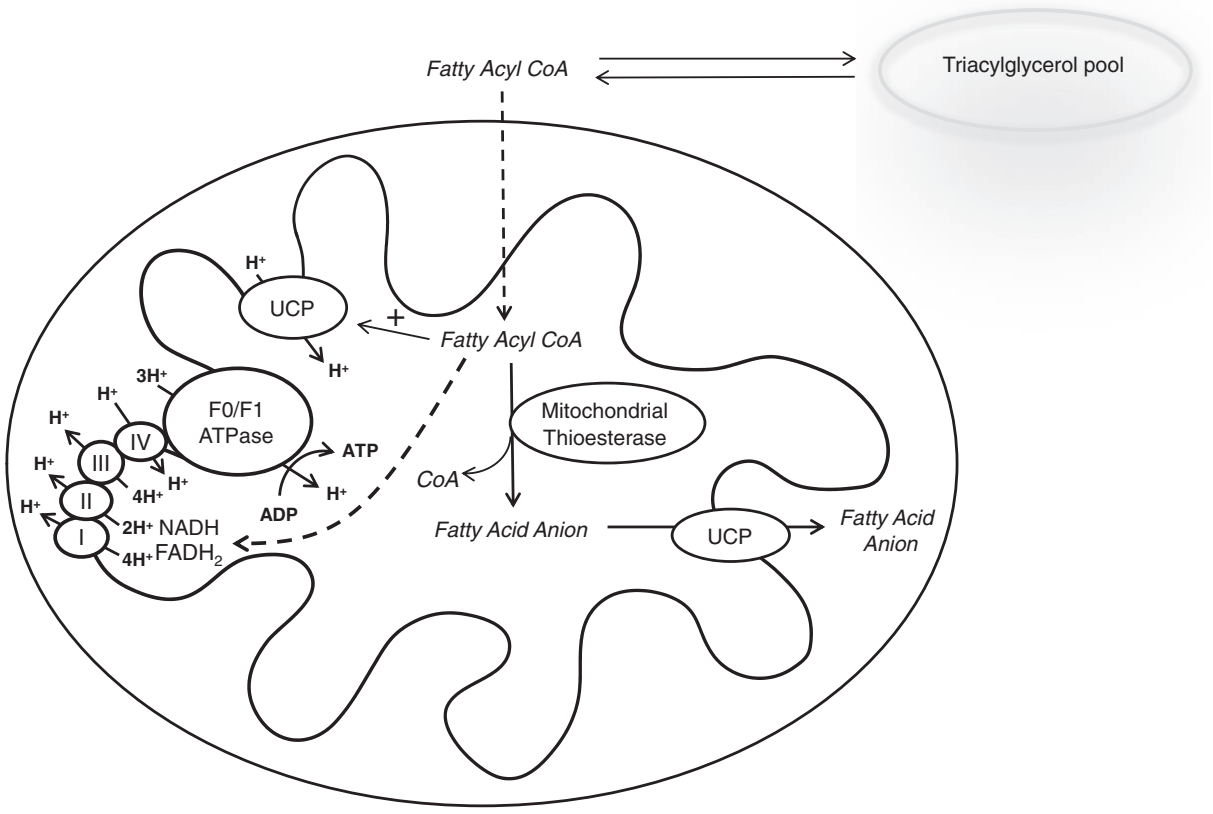

Fig. 2. Fatty acid-induced futile cycling in the heart. Fatty acids can decrease cardiac efficiency through a number of futile cycles. The cycling of fatty acids between long chain acyl CoA and triacylglycerol uses ATP. Efficiency of ATP production can also potentially be reduced by uncoupling the mitochondrial proton gradient due to increased uncoupling protein (UCP) activity. Mitochondrial thioesterase cleavage of long chain acyl CoA and the transport of fatty acid out of the mitochondria also results in a futile cycling that increases ATP use.

oxidation and increasing glucose oxidation appears particularly promising [23]. These targets include modifying fatty acid β-oxidation, decreasing levels of circulating fatty acids, and stimulating PDH (Fig. 3). Potential therapeutic strategies are likely to vary depending on the stage of heart failure, since the function of mitochondria is reduced in severe heart failure, which indicates that reducing fatty acid oxidation could be deleterious due to a decrease in the limited capacity to generate ATP [3,23]. In addition, it has been suggested that reducing circulating fatty acids can reduce cardiac function in the failing heart, indicating the importance of fatty acid as a substrate [67]. It may therefore be more beneficial in severe heart failure to target an overall increase in oxidative metabolism, such as increasing glucose oxidation as opposed to inhibiting fatty acid oxidation. This supports the hypothesis that the failing heart has low energy levels and any increase in energy supply would be beneficial. However, numerous other experimental and clinical studies have shown that inhibiting fatty acid oxidation can improve the function and efficiency of the failing heart. Discrepancies in reported results may be explained by studies being conducted at different stages of heart failure and/or causes of heart failure.

4.1. β-Adrenoceptor antagonists

β-Adrenoceptor antagonists are an important therapy used to treat heart failure. The negative inotropic and chronotropic effects of β-adrenoceptor antagonists reduce cardiac workload and increase oxygen sparing, which are the major reasons these drugs are used to treat heart failure [23]. However, inhibition of CPT1 activity, increased glucose oxidation, and increased efficiency of oxygen utilization for ATP production may also be partially responsible for the beneficial effect of β-adrenoceptor antagonists in heart failure [68,69]. β-Adrenoceptor antagonists improve left ventricle (LV) function without changing oxygen consumption, which indicates increased cardiac efficiency [23,70,71]. Carvedilol also reduces myocardial fatty acid uptake in heart failure patients [72]. In addition, β-adrenoceptor antagonists can decrease circulating fatty acid levels by reducing catecholamine induced lipolysis at the level of adipose tissue [23]. However, metoprolol improves cardiac function despite not reducing circulating fatty acid levels [32].

4.2. PPAR agonists

Drugs that target the PPAR family of transcription factors may be beneficial in heart failure. PPARβ/δ is a transcription factor that regulates the expression of genes involved in fatty acid metabolism. Some of these genes include FACS, CPT1, LCAD, and MCAD [73–75]. By increasing the expression of these genes PPARβ/δ can increase fatty acid oxidation and overall fatty acid utilization [73,75–77]. In cardiomyocytes PPARβ/δ have been reported to prevent hypertrophy induced down-regulation of fatty acid β-oxidation and expression of genes involved in fatty acid metabolism [76,77]. In addition, PPARβ/δ regulates expression of proteins involved in glucose metabolism. These genes include GLUT1, GLUT4, PFK1, and hexokinase 2 [78]. Furthermore, PPARβ/δ specific cardiac overexpression increases cardiac glucose oxidation rates [78]. Together, these results suggest that therapeutically increasing PPARβ/δ activity may be beneficial in the setting of heart failure by at least partially preventing the decrease in oxidative metabolism observed in heart failure [23].

The thiazolidinedione (TZD) class of drugs targets PPARγ. TZDs decrease circulating fatty acids and triacylglycerol levels, increase myocardial lactate uptake and oxidation, and increase myocardial glucose oxidation [79–81]. These results suggest that TZDs improve cardiac efficiency. However, there is evidence that increasing PPARγ activity could also be detrimental to heart function in heart failure patients. Safety concerns have been raised by clinical trials testing TZD therapy for heart failure in diabetics. The exacerbated heart failure in diabetic patients has been suggested to be due to vascular permeability and fluid retention [82]. In addition, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) Study reported that treatment with the PPARγ agonist pioglitazone increase heart failure incidence [83]. Meta-analysis suggest that rosiglitazone also increases the risk of myocardial infarction but not overall mortality due to cardiovascular events [84,85]. The ongoing Rosiglitazone Evaluated for Cardiac

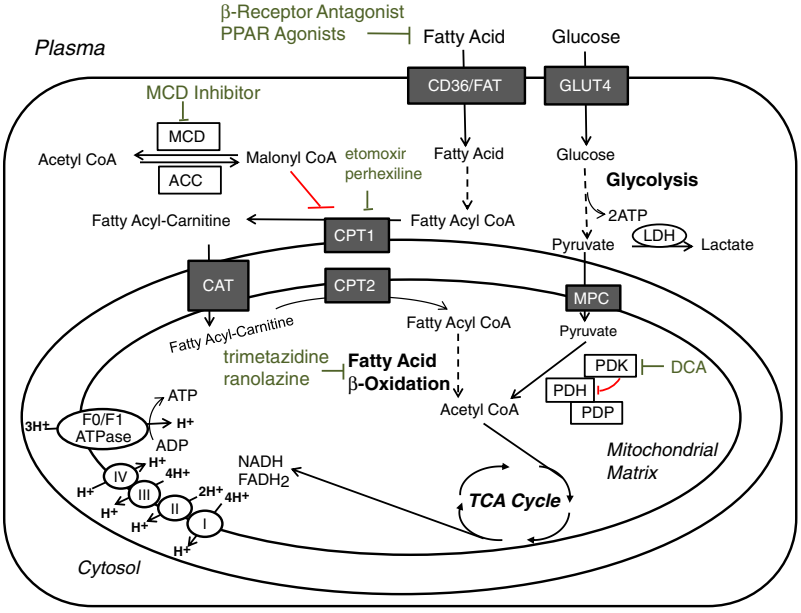

Fig. 3. Metabolic targets for the treatment of heart failure. β-Adrenoreceptor antagonists and PPAR agonists decrease the level of circulating fatty acids. Carnitine palmitoyltransferase I (CPT1) inhibitors decrease fatty acid β-oxidation and increase glucose oxidation by decreasing fatty acid transport into the mitochondria. Malonyl CoA decarboxylase (MCD) inhibition also decreases CPT1 activity by increasing malonyl CoA inhibition of CPT1. Trimetazidine and ranolazine can directly inhibit fatty acid β-oxidation. Dichloroacetate (DCA) increases glucose oxidation by inhibiting pyruvate dehydrogenase kinase (PDK) activity and thereby stimulating pyruvate dehydrogenase (PDH).

Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial has also reported that rosiglitazone increases the risk of heart failure [86].

Fibrates are a group of PPARα agonist drugs. They are believed to work by lowering circulating fatty acid levels via increasing extracardiac fatty acid oxidation [87,88]. The decreased fatty acid supply would result in decreased heart fatty acid oxidation. It has been reported that the PPAR alpha agonists protect against ischemia/reperfusion injury [89]. However, clinical trials have reported mixed results for fibrate treatment. Fenofibrate was beneficial in the Helsinki Heart Study and the VA-HIT trial but in the FIELD study there was no reduction in coronary heart disease mortality [90–92].

4.3. Fatty acid uptake into mitochondria

The rate limiting enzyme for fatty acid β-oxidation, and thus a potential drug target for regulating mitochondrial fatty acid uptake, is CPT1 (Fig. 3). Drugs targeting CPT1 include etomoxir, an irreversible CPT1 inhibitor [93], and perhexiline. In diabetic rat hearts, etomoxir increases glucose oxidation and improves cardiac function [94,95]. Etomoxir also improves the ventricular function of hearts subjected to pressure overload [96]. It has been suggested that etomoxir is also beneficial in heart failure by increasing sarcoplasmic reticulum calcium uptake in hypertrophied hearts [97]. The results of clinical trials are less clear. While one clinical trial found that etomoxir improves the clinical status of heart patients and heart function [98], another clinical trial had to end early due to high liver transaminase levels despite evidence of an increase in exercise time [99]. Perhexiline is a CPT1 inhibitor that inhibits the cardiac, but not hepatic, isoform of CPT1. In chronic heart failure, perhexiline improves VO_2 max, left ventricular ejection fraction, and overall myocardial energetics [100,101]. In addition, the beneficial effects of β-adrenoceptor antagonists may be partially due to inhibition of CPT1 activity, increased glucose oxidation, and increased efficiency of oxygen utilization for ATP production [68,69]. Therefore, targeting CPT1 may be useful in treatment of heart failure.

4.4. Malonyl-CoA decarboxylase inhibitors

Malonyl CoA decarboxylase (MCD) inhibition leads to a rise in cardiac malonyl CoA levels which inhibit CPT1, thereby reducing mitochondrial fatty acid uptake. MCD inhibition results in a decrease in cardiac fatty acid oxidation, a rise in cardiac glucose oxidation, and an increase in insulin sensitivity [102–106]. It is has not been tested yet whether MCD inhibition is beneficial in heart failure but since there are beneficial effects of direct inhibition of CPT1, this indirect method of CPT1 inhibition may also be beneficial in heart failure.

4.5. Mitochondrial fatty acid oxidation inhibition

The enzymes involved in mitochondrial fatty acid β-oxidation could also be targeted for the treatment of heart failure. Two drugs that target fatty acid β-oxidation include trimetazidine, a competitive inhibitor of long chain 3-ketoacyl-CoA thiolase (KAT), and ranolazine [107,108]. Although it has been reported that trimetazidine does not inhibit 3-KAT activity in rat hearts [109], at relevant concentrations of the substrate for 3-KAT, trimetazidine is indeed a potent inhibitor of 3-KAT [108]. In hypertrophied hearts, trimetazidine reduces glycolysis and proton production, but does not affect fatty acid oxidation [110]. In heart failure patients, trimetazidine also further increases the effectiveness of treatment regimens, improving NYHA functional class, LV ejection fraction and end-diastolic function [111,112]. In idiopathic heart failure patients, not only does trimetazidine improve cardiac function, but it also improves whole body insulin sensitivity [113].

Although ranolazine is marketed as a slow sodium current inhibitor, at clinically relevant concentrations, ranolazine is also a partial inhibitor of fatty acid oxidation [114–117]. Recently, it has also been suggested that a reduction in myofilament sensitivity is involved in ranolazine benefit in diastolic heart failure [118]. Ranolazine is currently being clinically used as an anti-ischemic agent. Ranolazine treatment does result in increased PDH activity and glucose oxidation [114–117]. Not surprisingly, ranolazine is also known to increase the coupling of glycolysis to glucose oxidation [115,116]. Interesting, ranolazine also inhibits the electron transport chain in damaged or uncoupled mitochondria, preventing ATP wasting due to futile cycling [119]. It is therefore more likely that inhibition of fatty acid oxidation and subsequent increased glycolysis glucose oxidation coupling is responsible for the beneficial effects of ranolazine in heart failure. Improved cardiac function has been reported in a canine model upon ranolazine administration [119,120]. Three months of ranolazine treatment prevented further LV remodeling and reduction in contractile function [121]. The efficacy of ranolazine in heart failure patients with preserved ejection fraction is currently now being examined in a small clinical study [122].

4.6. Pyruvate dehydrogenase kinase inhibitors

Directly increasing glucose oxidation is another potential strategy to treat heart failure. Dichloroacetate (DCA) increases PDH activity by inhibiting PDK, thereby increasing glucose oxidation (Fig. 3). This mechanism is responsible for the cardioprotection observed with DCA treatment [48,123]. In a study conducted in Dahl Sensitive rats DCA reduced LV hypertrophy progression to heart failure [45]. Other PDK inhibitors include SDZ048-619 and AZD7545, a selective inhibitor of PDK2. In the diabetic Zucker rat it has been shown that SDZ048-619 increases PDH activity in the liver, kidney, skeletal, and cardiac muscle [124,125]. AZD7545 increases PDH activity in the liver and, to a lesser extent, in skeletal and cardiac muscle [126]. While more work needs to be done to confirm that SDZ048-619 and AZD7545 increase cardiac glucose oxidation, these drugs are promising future agents for both therapeutic use and for scientific research.

4.7. Medium chain fatty acids

Medium chain fatty acids (MCFAs) are regulated in a different manner than long chain fatty acids [127]. MCFAs can cross the sarcolemmal and mitochondrial membranes independent of protein transport, bypassing any regulatory effects of CPT1 in their transport into mitochondria and/or oxidation in mitochondria. MCFAs are also believed to be preferentially used in fatty acid oxidation, as opposed to being stored as triacylglycerol. Because the cycling between triacylglycerol and fatty acid CoAs is an ATP consuming process [128], the reduction in futile cycling could potentially be useful in conditions of impaired ability to produce ATP, such as heart failure. MCFAs have not been examined in the failing heart. In the spontaneously hypertensive rat, MCFA dietary supplementation improves cardiac function, reduces cardiac hypertrophy, improves elevated insulin levels, and blocks progression of LV diastolic pressure [129–131]. Because MCFAs prevent both the reduction in MCAD expression and increase in PFK1 protein expression [130] in cardiac hypertrophy it has been suggested that MCFAs may prevent the reduced oxidative metabolism and increased glycolysis observed in the hypertrophied heart [23].

5. Limitation of metabolic modulation for treating heart failure

While regulating energy metabolism in the failing heart appears to be therapeutically beneficial in the treatment of heart failure, some aspects need to be considered to prevent potential problems with such a strategy. One such problem is that if fatty acids do not undergo fatty acid β-oxidation they may be used in the production of triacylglycerol, diacylglycerol, and ceramides [2,132]. The accumulation of these lipid metabolites has been proposed to cause “cardiac lipotoxicity”, which may induce a number of cardiac problems including impaired diastolic filling, cardiomyocyte cell death, LV chamber enlargement, and fibrosis

of myocardial tissue [3,133–139]. Stimulation of glucose oxidation could also cause such problems since, via the reverse Randle cycle, fatty acid β-oxidation would also be inhibited, which could lead to triacylglycerol accumulation [140]. However, there is evidence that triacylglycerol accumulation is not associated with cardiac dysfunction suggesting that its accumulation is not involved in "cardiac lipotoxicity" [141,142]. In fact, hearts from mice in which fatty acid oxidation is elevated due to cardiac specific deletion of ACC2 are protected against myocardial hypertrophy [143]. This perhaps suggests that chronic upregulation of fatty acid oxidation is protective because it prevents increases in lipid metabolites suggested to be involved in "cardiac lipotoxicity."

6. Conclusions

Mitochondrial oxidative metabolism is a promising target for the treatment of heart failure. An effective strategy appears to be inhibition of fatty acid oxidation and increasing the coupling of glycolysis to glucose oxidation. In order to achieve this, targets could include CPT1, fatty acid β-oxidation enzymes, and PDK. Modulating energy metabolism has the potential to improve cardiac function by improving the efficiency with which the heart utilizes ATP. This could lessen the energetic deficiency in ATP that can occur as the heart fails. Further, clinical and experimental studies are required to confirm the efficacy of targeting many of these metabolic proteins as an approach to treating heart failure.

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