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REVIEW

Mitochondrial fatty acid oxidation alterations in heart failure, ischaemic heart disease and diabetic cardiomyopathy

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Heart disease is a leading cause of death worldwide. In many forms of heart disease, including heart failure, ischaemic heart disease and diabetic cardiomyopathies, changes in cardiac mitochondrial energy metabolism contribute to contractile dysfunction and to a decrease in cardiac efficiency. Specific metabolic changes include a relative increase in cardiac fatty acid oxidation rates and an uncoupling of glycolysis from glucose oxidation. In heart failure, overall mitochondrial oxidative metabolism can be impaired while, in ischaemic heart disease, energy production is impaired due to a limitation of oxygen supply. In both of these conditions, residual mitochondrial fatty acid oxidation dominates over mitochondrial glucose oxidation. In diabetes, the ratio of cardiac fatty acid oxidation to glucose oxidation also increases, although primarily due to an increase in fatty acid oxidation and an inhibition of glucose oxidation. Recent evidence suggests that therapeutically regulating cardiac energy metabolism by reducing fatty acid oxidation and/or increasing glucose oxidation can improve cardiac function of the ischaemic heart, the failing heart and in diabetic cardiomyopathies. In this article, we review the cardiac mitochondrial energy metabolic changes that occur in these forms of heart disease, what role alterations in mitochondrial fatty acid oxidation have in contributing to cardiac dysfunction and the potential for targeting fatty acid oxidation to treat these forms of heart disease.

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Abbreviations
ACC, acetyl CoA carboxylase; CPT-1, carnitine palmitoyl transeferase 1; FABP, fatty acid binding protein; KO, knockout; LCAD, long-chain acyl CoA dehydrogenase; MCAD, medium-chain acyl CoA dehydrogenase; MCD, malonyl CoA decarboxylase; PDH, pyruvate dehydrogenase; PDK4, pyruvate dehydrogenase kinase 4; PGC-1α, PPARγ co-activator-1α; TAC, transverse aortic constriction; TG, triacylglycerol; TZD, thiazolidinediones

Introduction

Alterations in mitochondrial energy metabolism are common in many forms of heart disease (Lopaschuk *et al.*, 2010). Mitochondrial dysfunction and impaired energy production have been observed in many forms of heart disease, which include heart failure, ischaemic heart disease and diabetic cardiomyopathies (Beer *et al.*, 2002; Liu *et al.*, 2002; Lopaschuk *et al.*, 2010). In addition, the relationship between mitochondrial fatty acid oxidation and glucose oxidation can be altered in these forms of heart disease (Liu *et al.*, 2002; Buchanan *et al.*, 2005; Lopaschuk *et al.*, 2010). This includes an increase in the relative proportion of fatty acids oxidized by the mitochondria compared to carbohydrates oxidized (Liu *et al.*, 2002; Buchanan *et al.*, 2005; Lopaschuk *et al.*, 2010). Increases in the amount of fatty acid oxidized by the mitochondria in relation to carbohydrate oxidation has the potential to decrease cardiac efficiency and can contribute to the observed impaired heart function seen in heart failure, ischaemic heart disease and diabetic cardiomyopathies. Interestingly, there is accumulating evidence that modulating cardiac energy metabolism by increasing glucose oxidation directly, or indirectly by inhibiting fatty acid oxidation, can improve heart function. Some of the approaches used in basic and clinical studies to achieve this metabolic effect include PPARα agonists (Schoonjans *et al.*, 1993; Rubins *et al.*, 1999; Rubins

et al., 2002; Yue *et al.*, 2003; Keech *et al.*, 2005), fatty acid oxidation inhibitors such as trimetazidine (Saeedi *et al.*, 2005; Fragasso *et al.*, 2006a,b), mitochondrial fatty acid uptake inhibitors such as perhexiline and malonyl CoA decarboxylase (MCD) inhibitors and activators of pyruvate dehydrogenase (PDH), the rate-limiting enzyme involved in glucose oxidation such as dichloroacetate (Dyck *et al.*, 2004; Stanley *et al.*, 2005; Cheng *et al.*, 2006; Lopaschuk *et al.*, 2010). In this review, we focus on the mechanisms regulating cardiac fatty acid oxidation, the role of fatty acid oxidation in cardiac disease (with a focus on heart failure, ischaemic heart disease and diabetic cardiomyopathy), and the potential for fatty acid oxidation inhibition to treat cardiac disease.

Cardiac fatty acid oxidation

The energy substrates primarily used by the heart include fatty acids and carbohydrates (Lopaschuk *et al.*, 2010). Fatty acids are the main energy substrate of the heart and provide the majority of cofactors necessary for mitochondrial oxidative phosphorylation (Figure 1). Fatty acids enter the cell via fatty acid transporters on the cell membrane, which include tissue specific fatty acid transporter proteins, CD36/FAT and fatty acid binding protein (FABP) (Lopaschuk *et al.*, 2010). A CoA group is then added to the fatty acid by fatty acyl CoA synthetase allowing long-chain fatty acids to enter the mitochondria. This process includes carnitine palmitoyl transferase 1 (CPT-1) converting the long-chain fatty acyl CoA to an acyl carnitine, allowing entry into the mitochondria. Carnitine translocase then transports the long-chain fatty acyl carnitine across the inner mitochondrial membrane. The long-chain fatty acyl carnitine is then converted back to a fatty acyl CoA, which then enters fatty acid oxidation. Medium-chain fatty acids do not require these proteins to enter the mitochondria. Each cycle through fatty acid oxidation produces an acetyl CoA, NADH and $FADH_2$. The electron transport chain utilizes the NADH and $FADH_2$ produced by

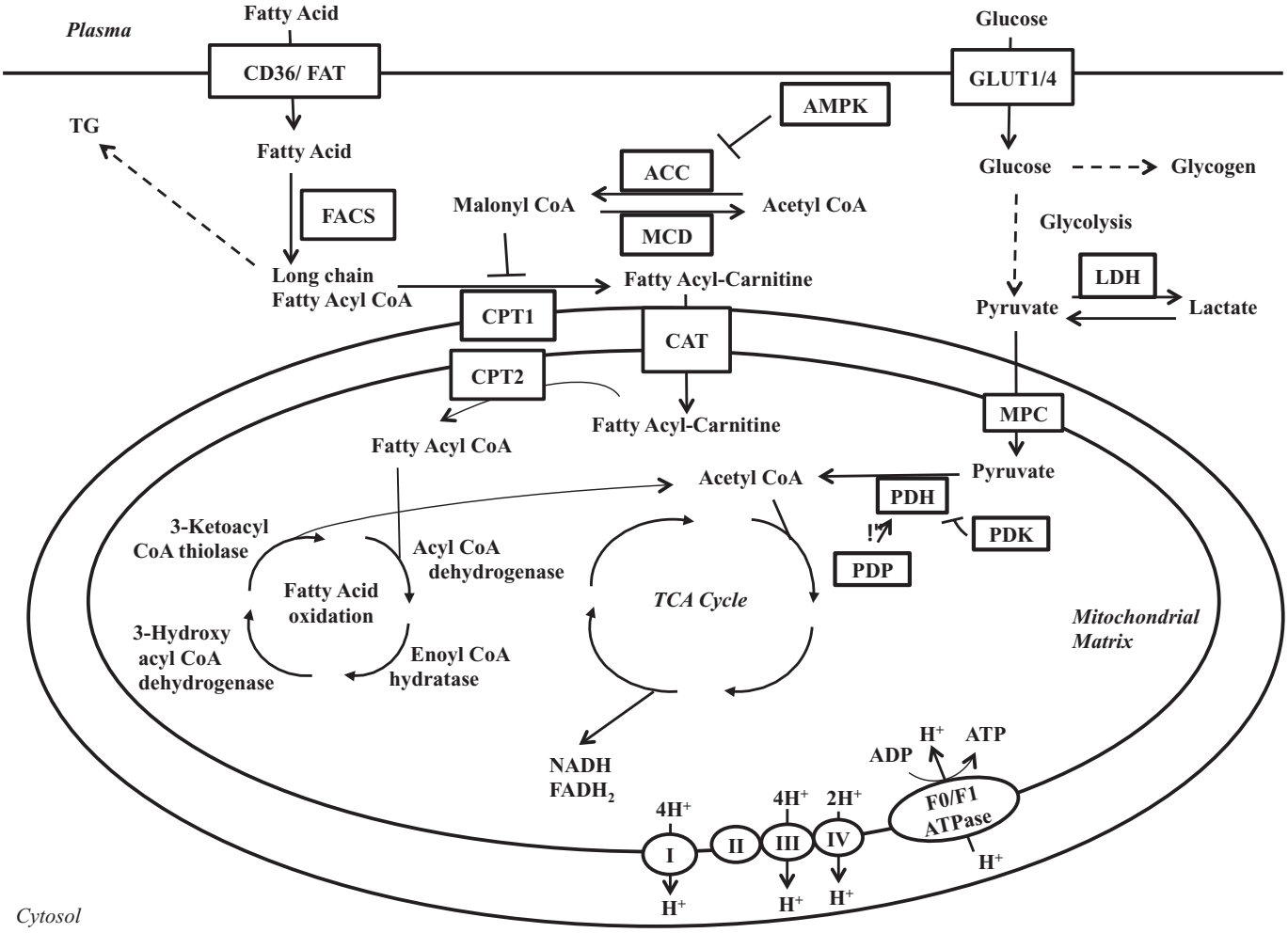

Figure 1

Overview of fatty acid and glucose oxidation in the heart. ACC, acetyl CoA carboxylase; AMPK, AMP- activated protein kinase; CPT, carnitine palmitoyl transferase; CAT, carnitine translocase; FACS, fatty acyl CoA synthetase; FAT, fatty acid transporter; GLUT, glucose transporter; LDH, lactate dehydrogenase; MCD, malonyl CoA decarboxylase; MPC, mitochondrial pyruvate carrier; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PDP, pyruvate dehydrogenase phosphatase; TCA, tricarboxylic acid; TG, triacylglycerol.

fatty acid oxidation, glucose oxidation, glycolysis and the tricarboxylic acid cycle in the production of ATP.

A number of factors regulate fatty acid oxidation including malonyl CoA and the glucose/fatty acid cycle. Malonyl CoA regulates fatty acid oxidation by inhibiting the first protein involved in mitochondrial long-chain fatty acid uptake, CPT-1 (McGarry *et al.*, 1977; 1978; Paulson *et al.*, 1984). Malonyl CoA and acetyl CoA levels are primarily regulated by two proteins, acetyl CoA carboxylase (ACC) and MCD. ACC produces malonyl CoA by carboxylation of acetyl CoA. MCD converts malonyl CoA back to acetyl CoA. Therefore, inhibition of MCD would be expected to decrease CPT-1 activity and subsequently decrease fatty acid oxidation by increasing the level of malonyl CoA while decreased ACC activity would be expected to have the opposite effect (Dyck *et al.*, 2004; Kolwicz *et al.*, 2012; Ussher *et al.*, 2012b). In fact, MCD inhibition has been shown to decrease cardiac fatty acid oxidation and improve cardiac function (Dyck *et al.*, 2004; Ussher *et al.*, 2012b).

Glucose is another major energy substrate of the heart, with glucose passing through glycolysis to produce pyruvate, which is taken up the mitochondria and converted to acetyl CoA and NADH by the rate-limiting enzyme of glucose oxidation, PDH. Fatty acid and glucose metabolism inter-regulate each other, a process referred to as the Randle Cycle or the glucose/fatty acid cycle (Randle *et al.*, 1963). Increasing fatty acid oxidation in the heart decreases glucose oxidation, while increasing glucose oxidation inhibits fatty acid oxidation. Fatty acid oxidation decreases glucose metabolism through a few mechanisms. PDH is inhibited by NADH and acetyl CoA produced from fatty acid oxidation (Sugden and Holness, 2003; Jaswal *et al.*, 2011). In addition, increased citrate levels can inhibit the glycolytic enzyme phosphofructokinase 1 and indirectly inhibit hexokinase through elevating glucose-6-phosphate levels (Randle *et al.*, 1970; Lopaschuk *et al.*, 2010). This further shift towards a greater percentage of the cardiac energy being derived from fatty acid oxidation, which is a less efficient source of energy than glucose oxidation (with regard to ATP produced per O_2 molecules consumed), helps explain why elevated fatty acid oxidation rates reduce cardiac efficiency.

As mentioned, increased glucose oxidation can also inhibit fatty acid oxidation. The fatty acid oxidation enzyme 3-ketoacyl CoA thiolase is inhibited by acetyl CoA produced from PDH (Olowe and Schulz, 1980). In addition, NADH produced from glucose oxidation inhibits 3-hydroxy acyl CoA dehydrogenase, one of the fatty acid oxidation enzymes (Eaton *et al.*, 1998). Because the amount of ATP produced per O_2 consumed is greater with when glucose is oxidized compared to fatty acids, fatty acids are a less efficient energy substrate than glucose. Six O_2 are consumed and 31 ATP are produced from the full oxidation of one glucose molecule. Oxidation of one palmitate consumes 23 O_2 while only producing 105 ATP. Since this mechanism only accounts for 10% of the reduction in cardiac efficiency but elevated fatty acid oxidation can result in up to a 30% decrease in cardiac efficiency, other mechanisms are also involved in the reduction in cardiac efficiency observed in hearts with elevated rates of fatty acid oxidation (Lopaschuk *et al.*, 2010). These mechanisms include uncoupling proteins and increased triacylglycerol (TG) cycling (Lopaschuk *et al.*, 2010).

Fatty acid oxidation in heart disease

Alterations in cardiac energy metabolism vary depending on the type of cardiac disease. While there is some confusion as to what happens to fatty acid oxidation in these different forms of heart disease, in general fatty acid oxidation rates are either increased, or increased in relation to glucose oxidation rates. This is believed to at least partially contribute to impaired heart function because the use of fatty acids for ATP production decreases cardiac efficiency. The alterations in fatty acid oxidation and causes of the altered fatty acid oxidation that occur in heart failure, ischaemic heart disease and diabetic cardiomyopathy are discussed below.

Heart failure

Both a deficit in energy production and alterations in the source of energy substrates are believed to be involved in the impaired cardiac function of failing hearts (Figure 2). The role of energy metabolism in heart failure and common diseases that lead to the development of heart failure, myocardial ischaemia and diabetic cardiomyopathy are discussed below. In heart failure, mitochondrial oxidative metabolism is reduced resulting in a 30–40% decrease in ATP levels and large decrease in phosphocreatine levels in the heart (Conway *et al.*, 1991; Nascimben *et al.*, 1995; Tian *et al.*, 1996; Neubauer *et al.*, 1999; Beer *et al.*, 2002). This is primarily due to the development of mitochondrial dysfunction, and an associated decrease in mitochondrial respiration. The magnitude of this decrease in mitochondrial function depends on the particular stage of heart failure and cause of heart failure (Lopaschuk *et al.*, 2010). In an attempt to compensate for the decrease in mitochondrial oxidative metabolism, glycolysis rates are elevated (Lei *et al.*, 2004; Degens *et al.*, 2006; Kato *et al.*, 2010; Lopaschuk *et al.*, 2010). These metabolic changes are consistent with the failing heart shifting back towards a fetal energy metabolism, which is characterized by a low capacity for mitochondrial oxidative metabolism and increased glycolysis (Beer *et al.*, 2002; Lei *et al.*, 2004; Degens *et al.*, 2006; Kato *et al.*, 2010; Lopaschuk *et al.*, 2010). In hypertrophied hearts due to pressure overload, this change in overall metabolic rates is accompanied by changes in expression and activity of transcriptional proteins such as hypoxia-inducible factor-1α (increased), PPARα (decreased) and PPARγ co-activator-1 (PGC-1)α (decreased) (el Alaoui-Talibi *et al.*, 1992; Allard *et al.*, 1994; Keller *et al.*, 1995; Morissette *et al.*, 2003; Lopaschuk *et al.*, 2010). Combined, this favours an increase in glycolysis and a decrease in mitochondrial oxidative metabolism. While decreased mitochondrial oxidative metabolism is associated with a decrease in fatty acid oxidation rates, it is also associated with a decrease in glucose and lactate oxidation rates (Mori *et al.*, 2012; Zhabyeyev *et al.*, 2013; Zhang *et al.*, 2013). High glycolysis rates and low glucose oxidation rates can result in an increase in the uncoupling of glycolysis from glucose oxidation, resulting in the production of protons (Figure 2) (Dennis *et al.*, 1991; Lopaschuk *et al.*, 2010). This can result in a series of events that can alter ionic homeostasis and result in ATP being rerouted away from contractile function towards re-establishing ionic homeostasis, thereby decreasing cardiac efficiency (Figure 2).

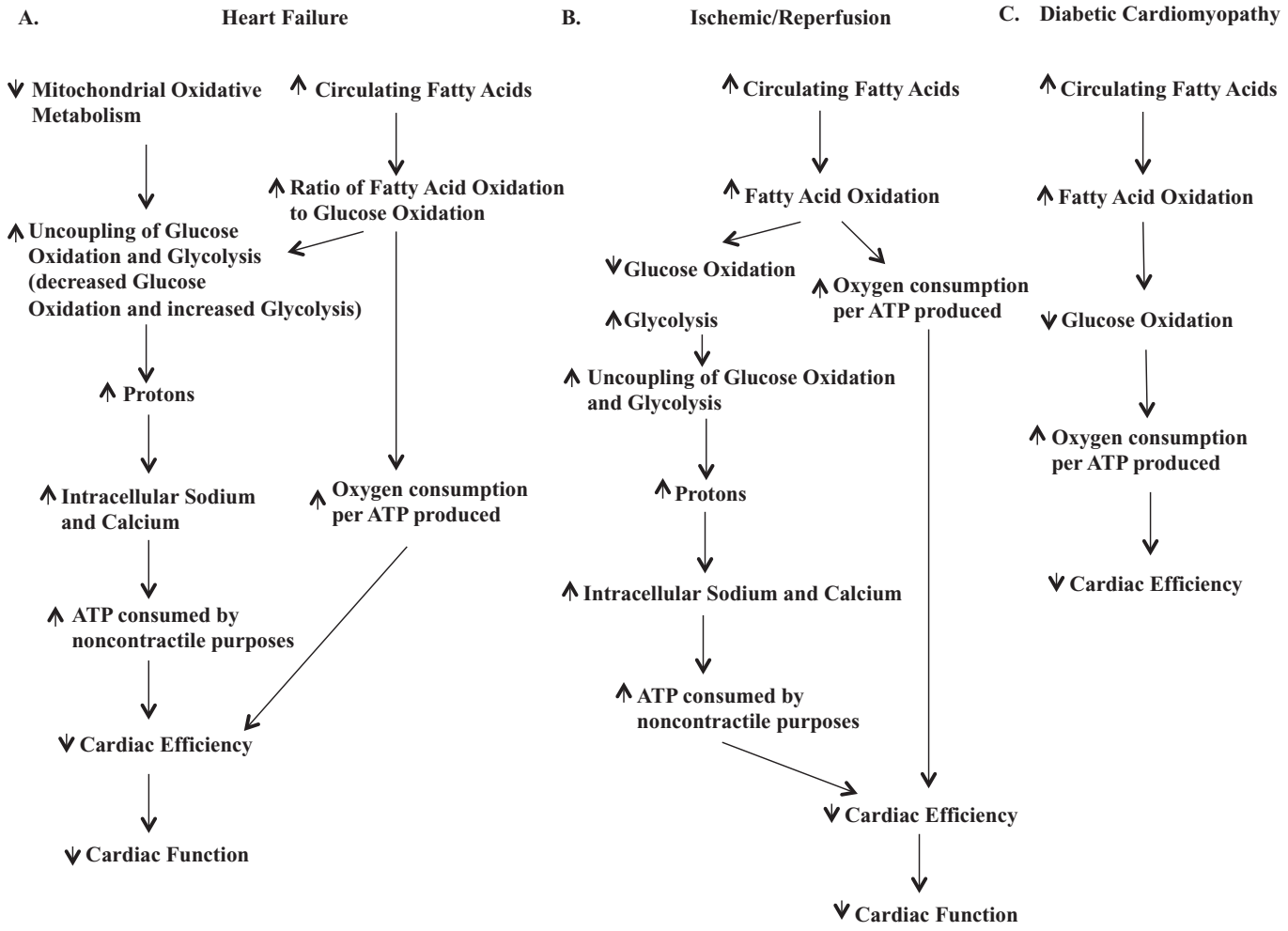

Figure 2

Diagram of how the alterations in fatty acid oxidation that occur in (A) heart failure, (B) ischaemic/reperfusion and (C) diabetic cardiomyopathy can lead to impaired cardiac function.

Angiotensin II has recently been implicated as a potential important regulator of cardiac energy metabolism and function (Mori *et al.*, 2012; 2013a,b). Angiotensin II is a main effector of the renin-angiotensin system. Activation of the renin-angiotensin system is associated with many pathological conditions, such as obesity, diabetes mellitus, heart failure and kidney disease. Inhibition of the renin-angiotensin system, such as with angiotensin converting enzyme inhibitors and angiotensin AT_1 receptor antagonists, is widely used in the clinical setting to treat heart disease. Angiotensin II damages mitochondria in the cardiomyocyte by increasing reactive oxygen species production (Dai *et al.*, 2011). Angiotensin II also affects mitochondrial oxidative phosphorylation, including fatty acid oxidation. Transgenic mice overexpressing angiotensinogen in the myocardium (TG1306/R1 mice), have reduced cardiac fatty acid oxidation rates concomitant with decreased expression of PPARα protein and fatty acid oxidation enzymes [medium-chain acyl CoA dehydrogenase (MCAD) and CPT-1] (Pellieux *et al.*, 2006). In cultures of adult rat cardiomyocytes, angiotensin II induces down-regulation of mRNA and protein expressions of genes involved in fatty acid oxidation (CD36, MCAD and CPT-1), which can be prevented by the anti-TNF-α antibody (Pellieux *et al.*, 2009). These data suggest that angiotensin II affects fatty acid oxidation, not glucose oxidation. However, evidence that angiotensin II regulates glucose oxidation is also accumulating (Mori *et al.*, 2012; 2013a). Angiotensin II probably reduces glucose oxidation by increasing pyruvate dehydrogenase kinase 4 (PDK4) expression, which would likely result in decreased PDH activity and a selective reduction of carbohydrate oxidation (Mori *et al.*, 2012). Angiotensin II-induced elevation in PDK4 expression can also induce insulin resistance causing the heart to switch from using glucose to fatty acids for energy and resulting in decreased cardiac efficiency (Mori *et al.*, 2013a). These angiotensin II-induced alterations in cardiac energy metabolism precede diastolic dysfunction, suggesting that these perturbations in cardiac energy metabolism contribute to the development of diastolic dysfunction. Possible mechanisms through which angiotensin II causes diastolic dysfunction include elevating intracellular Ca^{2+} levels, due to intracellular acidosis caused by increased uncoupling of glycolysis and glucose oxidation.

This decreases cardiac efficiency because removal of the accumulating cytoplasmic calcium, which is necessary to maintain and achieve appropriate relaxation, is an ATP-consuming process. In addition, angiotensin II can reduce ATP levels by decreasing oxidative metabolism, compromising ATP production.

Ischaemia/reperfusion

During ischaemia, overall mitochondrial oxidative metabolism decreases in proportion to the decrease in oxygen supply to the heart. During reperfusion of the ischaemic heart, overall cardiac fatty acid oxidation rates are elevated due, at least partially, to elevated circulating fatty acids (Folmes *et al.*, 2009). In addition, the subcellular control of fatty acid oxidation is altered, such that fatty acid oxidation becomes deregulated. This includes an ischaemic-induced decrease in malonyl CoA, which is normally a potent inhibitor of mitochondrial fatty acid uptake (Figure 1) (Kudo *et al.*, 1995). Elevated levels of circulating fatty acids combined with a decrease in malonyl CoA levels results in an increase in fatty acid oxidation rates during reperfusion, with a concomitant marked decrease in glucose oxidation rates (Figure 2). This has been described by the Randle cycle which states that elevated rates of fatty acid oxidation result in inhibition of glucose oxidation by inhibiting the activity of PDH. This elevation in circulating fatty acids and cardiac fatty acid oxidation during ischaemia/reperfusion supports the concept that fatty acid oxidation can impair cardiac function and efficiency especially during ischaemia/reperfusion (Figure 2) (Liu *et al.*, 2002). The decrease in glucose oxidation during ischaemia/reperfusion can result in increased uncoupling of glycolysis from glucose oxidation and a subsequent increase in production of lactate and protons which can decrease cardiac efficiency and impair heart function (Liu *et al.*, 2002).

Accumulation of protons and lactate decrease cardiac efficiency. This is because the mechanisms involved in removing these protons can lead to accumulation of intracellular calcium and sodium if ATP is not used to maintain ionic homeostasis (Dennis *et al.*, 1991; Lopaschuk *et al.*, 2010). This increased transarcolemmal proton gradient is dissipated by transportation of the protons out of the cell by the Na^+/H^+ exchanger. However, this exchanger simultaneously transports sodium into the cell. The Na^+/Ca^{2+} exchanger then starts working in reverse, resulting in influx of calcium as sodium intracellular levels are returned to normal. ATP is then used to transport the calcium out of the cell, maintaining normal intracellular calcium levels. The utilization of ATP to maintain ionic homeostasis reduces cardiac efficiency.

Diabetic cardiomyopathy

Diabetic cardiomyopathy is defined as ventricular dysfunction occurring in patients with diabetes mellitus, independent of other coronary artery diseases. Diabetes mellitus, one of the most common and costly chronic diseases, is also one of the most common causes of heart disease. According to recent epidemiological data, more than 25% of people over 65 years in the United States have diabetes mellitus. Cardiovascular disease is one of the severe complications, and the major cause of death, in patients with diabetes mellitus. In fact, diabetes mellitus doubles the likelihood of having a heart attack (Donnelly *et al.*, 2000). Alterations in cardiac mitochondrial energy metabolism are believed to contribute to the development of diabetic cardiomyopathies (How *et al.*, 2007; Onay-Besikci *et al.*, 2007; Sharma *et al.*, 2008; Rijzewijk *et al.*, 2009). For instance, hearts from animals or humans with diabetes mellitus or obesity are characterized by elevated fatty acid oxidation rates (Lopaschuk and Tsang, 1987; Mazumder *et al.*, 2004; Peterson *et al.*, 2004; Carley and Severson, 2005; Herrero *et al.*, 2006). This results in a marked decrease in glucose oxidation rates (Figure 2), resulting in mitochondrial fatty acid oxidation dominating as a source of energy in the diabetic or obese heart. These alterations in cardiac energy metabolism precede the development of glucose intolerance and cardiac hypertrophy (Buchanan *et al.*, 2005). While the role of energy metabolism is likely to be much more complex, it is becoming clear that excessively high fatty acid oxidation rates contribute to the abnormalities in energy metabolism and cardiac function observed in diabetic cardiomyopathy (How *et al.*, 2007; Onay-Besikci *et al.*, 2007; Sharma *et al.*, 2008).

The mechanism by which excessive fatty acids contribute to the development of diabetic cardiomyopathy could include both the accumulation of fatty acids in the heart, as well as high rates of fatty acid oxidation. Diabetes mellitus is commonly associated with cardiac lipotoxicity, which probably contributes to cardiac dysfunction. Fatty acids can be metabolized into fatty acid intermediates, such as diacylglycerol (DAG) and ceramides, which may contribute to cardiac insulin resistance and, subsequently, reduce cardiac function (Zhang *et al.*, 2010; 2011; Ussher *et al.*, 2012a). In the heart, DAG is believed to be the major lipid intermediate involved in insulin resistance (Zhang *et al.*, 2011). A number of studies have also shown an accumulation of myocardial TG in diabetes mellitus and obesity, although TG itself is not believed to contribute to myocardial insulin resistance (Zhang *et al.*, 2011). The mechanisms involved in the accumulation of these lipid intermediates remain obscure. There are two proposed scenarios to explain the accumulation of intramyocardial lipid: (i) impaired fatty acid oxidation, and (ii) oversupply of fatty acids.

The idea that impaired mitochondrial fatty acid oxidation induces the accumulation of intramyocardial lipid has not been consistently supported (Lopaschuk *et al.*, 2010). Most studies in animals (How *et al.*, 2007; Onay-Besikci *et al.*, 2007; Sharma *et al.*, 2008) and humans (Rijzewijk *et al.*, 2009; Peterson *et al.*, 2012) have shown that myocardial fatty acid oxidation rates are high in the diabetic. Similarly, in obesity, fatty acid oxidation rates are also elevated (Peterson *et al.*, 2004; Axelsen *et al.*, 2012).

A more likely explanation for the accumulation of lipids in the diabetic myocardium is due to the elevated levels of circulating fatty acids commonly seen in diabetes (How *et al.*, 2007; Peterson *et al.*, 2012). A number of factors, including elevated levels of insulin, contribute to these high levels of circulating fatty acids. Insulin inhibits lipolysis in adipose tissue and accelerates TG synthesis. In the setting of insulin resistance, such as Type 2 diabetes, lipolysis in adipose tissue and hydrolysis of TG are increased leading to elevated levels of circulating free fatty acids.

Cellular fatty acid uptake is another contributing factor in the high fatty acid supply to the heart in diabetic

cardiomyopathy. Cardiac insulin resistance is accompanied by a persistent relocation of the fatty acid transporters CD36 and FABP from the cytosol to the cell membrane (Luiken *et al.*, 2001; Coort *et al.*, 2004; Carley *et al.*, 2007). Persistent relocation of CD36 or FABP fatty acid transporters leads to a chronic elevation in fatty acid uptake, which could contribute to the increased cardiac fatty acid oxidation observed in diabetic hearts (Chabowski *et al.*, 2005). At 4 weeks of age, *db/db* mice already have elevated cardiac fatty acid oxidation and reduced cardiac glucose oxidation rates (Buchanan *et al.*, 2005). Genetic studies also indicate a role for proteins involved in fatty acid uptake playing a role in the progression of diabetic cardiomyopathy. For example, reducing the FABP expression decreases the severity of high fat diet-induced cardiac insulin resistance (Shearer *et al.*, 2008). Importantly, this partial knockdown of FABP3 expression did not have deleterious effects on cardiac function (Shearer *et al.*, 2008). In addition, overexpression of other proteins involved in fatty acid uptake, such as long-chain acyl-CoA synthetase and lipoprotein lipase, produces lipotoxic cardiomyopathy (Chiu *et al.*, 2001; Yagyu *et al.*, 2003).

The PPARs also play a role in these alterations in cardiac fatty acid metabolism. Fatty acids are endogenous ligands of the PPAR family. Fatty acids and their derivatives increase the expression of genes regulated by the PPARs, which include enzymes involved in fatty acid oxidation. PPARα augments the expression of CD36, CPT-1, MCD, and long-chain acyl CoA dehydrogenase (LCAD), resulting in increased mitochondrial fatty acid oxidation rates in the heart (Yang and Li, 2007). PPARα expression is enhanced in insulin resistance and diabetes mellitus, which suggests that this transcription factor may play a role in the elevated fatty acid transport and oxidation observed in diabetic hearts (Finck *et al.*, 2002; Buchanan *et al.*, 2005). Further, the phenotype of PPARα overexpressing mice resembles Type 2 diabetes mellitus and is accompanied by enhanced fatty acid oxidation rates (Finck *et al.*, 2002). On the other hand, other studies have shown that in *db/db* mice aged 15–18 weeks the expression of PPARα is not enhanced, although the expression of PPARα-regulated genes, such as MCAD, LCAD and mCPT-1, are increased (Finck *et al.*, 2002; Buchanan *et al.*, 2005; Daniels *et al.*, 2010). The lack of change in the expression of PPARα may suggest that alterations in cardiac metabolism in *db/db* mice are independent of PPARα, or it may suggest that PPARα activity is enhanced independent of protein expression. The expression of the PPARα co-activator, PGC-1, is enhanced in *db/db* mice, eventually leading to increased PPARα activity (Carley and Severson, 2005). PPARα also modifies the expression of PDK4, which phosphorylates PDH and inhibits the rate of glucose oxidation. Activation of PPARα reduces glucose oxidation rates, contributing to the high mitochondrial fatty acid oxidation rates (via the Randle cycle). This is a potential mechanism for the altered energy metabolism in diabetic hearts. This oversupply of fatty acids and subsequent activation of the PPARs plays a critical role in the increased cardiac fatty acid oxidation observed in diabetes mellitus.

Overall, the data suggest that, in diabetic cardiomyopathy, oversupply of fatty acids is responsible for the observed cardiac lipotoxicity. The fatty acids might overwhelm the rate of fatty acid oxidation, leading to accumulation of lipid intermediates. This, however, would not be due directly to reduced fatty acid oxidation, since fatty acid oxidation rates do not decrease and, in most cases, increase in the setting of diabetes. It is important to also note that cardiac lipotoxicity could also be involved in other conditions where a long-term elevation of circulating fatty acids accompanies impaired heart function.

Targeting fatty acid oxidation to treat cardiac disease

Inhibition of mitochondrial fatty acid oxidation has proven to be a promising target for treatment of heart failure, ischaemic heart disease and diabetic cardiomyopathy. Fatty acid oxidation can be inhibited by either directly inhibiting fatty acid oxidation (i.e. decreasing fatty acid uptake into the mitochondria or inhibiting mitochondrial fatty acid oxidation) or indirectly by increasing glucose oxidation. Pharmacological inhibition of fatty acid oxidation with drugs such as MCD inhibitors (i.e. CBM-301106), CPT-1 inhibitors (i.e. perhexiline, etomoxir) or mitochondrial fatty acid oxidation inhibitors (i.e. trimetazidine) (Figure 3) is beneficial. Another approach to inhibiting fatty acid oxidation includes the use of PPARα or PPARγ ligands that decrease the circulating fatty acid supply to the heart (Figure 3). While these drugs will not be discussed, it is important to mention that another strategy to inhibit fatty acid oxidation is to increase glucose oxidation which results in inhibition of fatty acid oxidation (Figure 3). This should also be beneficial in severe heart failure because it is not directly inhibiting pathways producing ATP. Directly inhibiting fatty acid oxidation may decrease ATP levels, which are already reduced in severe heart failure, and reduce function of the failing heart. The fact that reducing fatty acid oxidation can improve cardiac function supports the concept that the elevated fatty acid oxidation rates observed in conditions such as reperfusion following ischaemia are part of the cause of impaired cardiac function.

Fatty acid oxidation inhibition has the potential to treat heart disease. One drug that directly targets mitochondrial fatty acid oxidation enzymes is trimetazidine. Trimetazidine improves the function of failing hearts and reduces rates of glycolysis and/or increases glucose oxidation resulting in reduced proton levels (Saeedi *et al.*, 2005; Fragasso *et al.*, 2006a,b). However, not all studies have reported a decrease in fatty acid oxidation rates in hearts treated with trimetazidine (Kantor *et al.*, 2000; Saeedi *et al.*, 2005). A contributing factor is probably that Kantor *et al.* who reported a drop in fatty acid oxidation rates, used 0.4 mM palmitate in the perfusate in their experiments but Saeedi *et al.* used 1.2 mM palmitate (Kantor *et al.*, 2000; Saeedi *et al.*, 2005). Because trimetazidine is a reversible competitive inhibitor of 3-ketoacyl CoA thiolase, high levels of this enzyme's substrate can overcome trimetazidine inhibition (Lopaschuk *et al.*, 2003).

MCD inhibitors also appear to be promising for the treatment of cardiac disease. MCD inhibition leads to increased glucose oxidation, decreased fatty acid oxidation and improved insulin sensitivity (Dyck *et al.*, 2004; Stanley *et al.*, 2005; Cheng *et al.*, 2006; Lopaschuk *et al.*, 2010). Inhibition

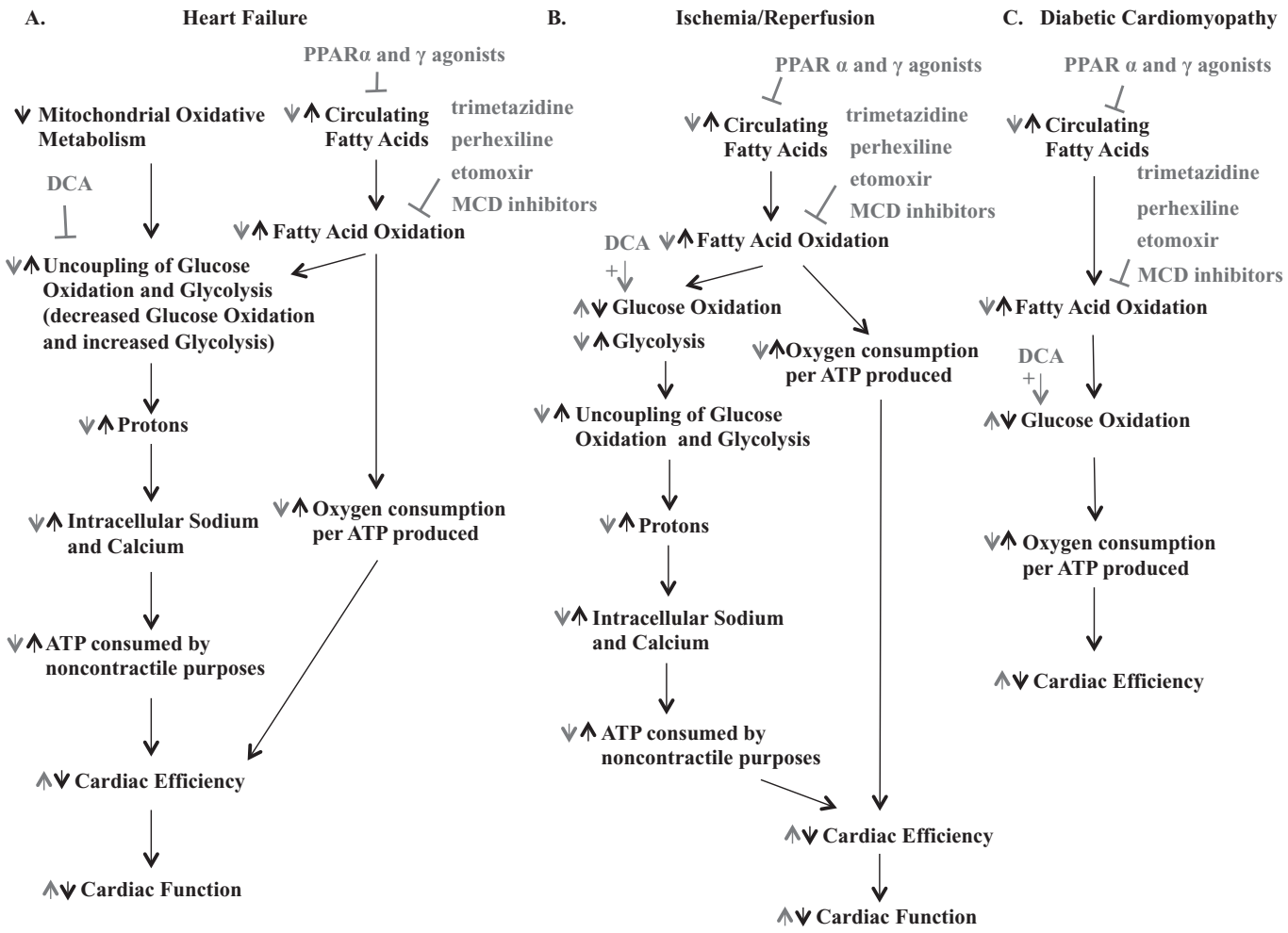

Figure 3

Diagrams of how drugs that inhibit fatty acid oxidation [trimetazidine, etomoxir, perhexiline, PPAR agonists and malonyl CoA decarboxylase (MCD) inhibitors] and increase glucose oxidation (dichloroacetate/DCA) improve cardiac function in (A) heart failure, (B) ischaemia/reperfusion and (C) diabetic cardiomyopathy.

of MCD leads to elevated malonyl CoA levels which inhibit CPT-1 and consequently decrease fatty acid oxidation rates. While the effects of MCD inhibition on heart failure have yet to be tested, the effects of MCD inhibition on cardiac energy metabolism suggest that MCD inhibition would be beneficial in the setting of heart failure.

PPARs are also being targeted to treat cardiac disease. Two classes of drugs that target the PPAR transcription factor family are fibrates and thiazolidinediones (TZD). PPARγ is activated by TZDs. TZDs have several beneficial effects including lowering circulating TG and fatty acid levels and increasing cardiac glucose oxidation, which should increase cardiac efficiency (Zhu *et al.*, 2000; Sidell *et al.*, 2002; Yue *et al.*, 2005). However, cardiac function may be impaired by TZDs. Diabetic patients treated with TZDs were reported to have exacerbated heart failure (Lindenfeld and Masoudi, 2007). In addition, heart failure incidence was greater in the diabetic patients treated with TZDs in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) Study (Dormandy *et al.*, 2005). These side effects could be the result of a number of factors including TZD stimulation of vasodilation leading to elevated peripheral oedema (Lindenfeld and Masoudi, 2007). Fibrates increase PPARα activity. The beneficial of effects of these drugs in the heart is believed to be due to decreased cardiac fatty acid oxidation due to reduced levels of circulating fatty acids (Schoonjans *et al.*, 1993; Cook *et al.*, 2000). Benefits from treating with PPARα agonists are mixed. They have been reported to protect the heart from ischaemia/reperfusion injury (Yue *et al.*, 2003). However, fibrates were beneficial in the Helinski Heart Study and Va-HIT trial but did not reduce coronary heart disease mortality in the FIELD study (Rubins *et al.*, 1999; 2002; Keech *et al.*, 2005). Increasing PPARδ activity is another promising strategy to treat cardiac disease. PPARδ increases the expression of many genes including some involved in fatty acid oxidation (Yang and Li, 2007). PPARδ has actually been reported to prevent cardiomyocyte hypertrophy (Planavila *et al.*, 2005; Pellieux *et al.*, 2009) and increase cardiac glucose oxidation rates (Burkart *et al.*, 2007). The beneficial effect of PPAR agonists in cardiac disease is somewhat paradoxical as they would be expected to

increase cardiac fatty acid oxidation, by increasing the expression of proteins involved in fatty acid oxidation which, as described earlier, is generally considered to decrease cardiac function. But by increasing extracardiac fatty acid oxidation, PPAR agonists decrease the level of circulating fatty acids which results in decreased cardiac fatty acid oxidation rates (Lopaschuk *et al.*, 2010).

While data to date suggest that there is an important role for fatty acid oxidation in cardiac disease progression and treatment, it is not completely straightforward. For example, recent work in the ACC2 knockout (KO) mouse does not directly support the concept that fatty acid oxidation reduces heart function (Kolwicz *et al.*, 2012). ACC2 KO mouse cardiac function is not only normal but is better post transverse aortic constriction (TAC) surgery compared to wild-type animals also subjected to TAC surgery (Kolwicz *et al.*, 2012). As mentioned previously, the mechanism by which elevated fatty acid oxidation impairs cardiac function may involve elevating glycolysis, increasing the uncoupling of glycolysis from glucose oxidation. ACC2 KO mice may have normal heart function because the amount of glycolysis uncoupled from glucose oxidation is not elevated despite elevated rates of fatty acid oxidation. There is also evidence that reducing cardiac fatty acid oxidation is detrimental in the failing heart. For example, reducing the level of circulating fatty acids further reduces cardiac function in heart failure despite the expected decrease in markers of fatty acid oxidation (Tuunanen *et al.*, 2006). Interestingly, there is data that suggest that a diet high in saturated fatty acids, which would be expected to elevate cardiac fatty acid oxidation rates, actually improves cardiac function in the setting of myocardial infarction while it is detrimental under non-pathological conditions (Berthiaume *et al.*, 2012). This high-fat diet also improves the function of failing hearts (Berthiaume *et al.*, 2010). Decreasing fatty acid oxidation is probably detrimental because it reduces ATP in a condition where ATP levels are already low.

Conclusion

Cardiac energy metabolism, especially fatty acid oxidation, appears to be an important factor in heart disease pathogenesis. While increases in mitochondrial fatty acid oxidation rates do not always accompany cardiac disease, its elevation does appear in many cases to be involved in the observed impaired heart function. It may be that the increased uncoupling of glycolysis from glucose oxidation resulting from fatty acid oxidation-induced inhibition of glucose oxidation is more commonly the cause of cardiac disease. In fact, in severe end-stage heart failure where fatty acid oxidation is actually decreased, the uncoupling of glycolysis from glucose oxidation is increased. As would be expected, drugs that increase glucose oxidation improve cardiac function. Nevertheless, fatty acid oxidation inhibition is a promising target for the treatment of cardiac disease. However, strategies aimed at treating heart disease by inhibiting fatty acid oxidation will need to be carefully considered, based on the specific cardiac disease, so as not to further exacerbate a condition where any reduction in ATP levels is detrimental.

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Conflict of interest

None.

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