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Perturbations in myocardial energy metabolism in the ischemic heart

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Abstract: As an organ that must continuously pump oxygenated blood throughout the body, the heart has an enormous metabolic demand, which is primarily met via oxidative metabolism of fatty acids and carbohydrates. Because of its high metabolic demand, during times of reduced oxygen supply such as ischemia, the heart becomes highly susceptible to injury, and if flow is not re-established, myocardial tissue is lost and can result in death (myocardial infarction). Of interest, both myocardial ischemia and reperfusion are associated with a number of perturbations in energy metabolism that contribute to the pathology of ischemic heart disease. This includes marked elevations in glycolysis to counteract the reduction in oxidative metabolism, whereas fatty acids predominate as the primary fuel source for residual oxidative metabolism. During the early stages of cardiac recovery after successful reperfusion of the ischemic heart, fatty acid oxidation rates also rapidly recover at the expense of low glucose oxidation rates. These metabolic perturbations increase myocardial acidosis due to glycolysis being uncoupled from glucose oxidation, which impairs cardiac efficiency. As such, therapeutic approaches to stimulate glucose oxidation or inhibit fatty acid oxidation have the potential to correct dysregulated myocardial energy metabolism during ischemia and reperfusion, which improves cardiac efficiency and may lead to improved clinical outcomes in people with ischemic heart disease. ■ *Heart Metab*. 2020;81:17-22

Keywords: cardiac energetics; fatty acid oxidation; glucose oxidation; ischemia; reperfusion

Introduction

The majority of the heart's energy (90% to 95%) is produced through oxidative metabolism in the mitochondria, with the remainder produced through glycolysis (5% to 10%).[1,2] Exogenous circulating fatty acids (eg, palmitate and oleate) and carbohydrates (eg, glucose) are the primary oxidative fuel sources for the heart, with fatty acids acting as the predominant fuel during times of fasting/starvation, and glucose becoming a more relevant fuel after nutrient ingestion.[3] Although complex molecular and hormonal control are involved (extensively reviewed by Lopaschuk et al[3]), the "Randle Cycle" phenomenon by which glucose and fatty acids compete for oxidative metabolism[4] also contributes to the myocardial energy metabolism profiles observed during fasting and nutrient ingestion. Endogenous triacylglycerol and glycogen stores can also support energy production in the heart, though these storage forms are minimal in

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supply.[5,6] Because of the heart's limited energy stores and the enormous energy demand needed to support constant pump function, the heart will metabolize virtually any energy substrate supplied throughout its coronary circulation (eg, fatty acids, glucose, lactate, ketones, amino acids).[1,2] Furthermore, the heart has the highest oxygen demand on a per-gram basis of all organs in the body, and is therefore highly susceptible to injury during conditions of reduced oxygen supply such as myocardial ischemia.

Myocardial ischemia is a major health disorder that occurs when there is a reduction in or complete block of blood and subsequent oxygen supply to the myocardium. This primarily occurs due to a blockage of the coronary artery due to the buildup of an atherosclerotic plaque, and/or an increase in oxygen demand due to an increase in cardiac work (eg, exercise or fight-or-flight response). Myocardial ischemia reduces oxygen supply, thereby disrupting mitochondrial oxidative metabolism and subsequent cardiac energy (adenosine triphosphate [ATP]) production, which compromises cardiac function. If coronary flow is not re-established, prolonged myocardial ischemia leads to the death of cardiac myocytes and loss of myocardial tissue (myocardial infarction). Despite the restoration of coronary flow during successful reperfusion of the ischemic myocardium, significant metabolic perturbations persist and can directly impact the recovery of cardiac function. We will herein discuss the metabolic perturbations that characterize both the ischemic and ischemic/reperfused myocardium, as well as the potential therapeutic approaches to optimize cardiac energy metabolism in ischemic heart disease.

Energy metabolism in the ischemic myocardium

As just alluded to, the most notable metabolic perturbation during myocardial ischemia is a marked impairment in oxidative energy metabolism due to the reduction in oxygen supply, with the impairment becoming more severe as the ischemia worsens. During ischemia of isolated working rat hearts where limited flow persists (low-flow ischemia), it has been shown that the majority of residual oxidative energy metabolism is accounted for by the oxidation of fatty acids.[7,8] In ischemic heart disease subjects undergoing coronary sinus and arterial catheterization, it has been shown that myocardial oleate uptake and oxidation are similar to that seen in healthy subjects, whereas myocardial palmitate uptake and oxidation showed trends of being elevated. Likewise, in humans with coronary artery disease and a history of myocardial infarction, it has also been demonstrated that myocardial glucose uptake rates are diminished and that the myocardium becomes insulin-resistant,[9] similar to what has been observed in the setting of heart failure.[3,10]

In an attempt to compensate for the reduction in cardiac energy production during myocardial ischemia, glycolysis is markedly upregulated to increase anaerobic ATP production. Increases in glycolysis in the ischemic myocardium are fueled by extracellular glucose, as well as the mobilization of endogenous glycogen stores. As myocardial ischemia persists and glycogen stores are depleted, or if the ischemia and reduction in flow worsens, glycolysis rates will eventually diminish or come to a halt with contractile activity ceasing.[11] This is partly due to increased myocardial lactate not being washed out, which inhibits the activity of glyceraldehyde-3-phosphate dehydrogenase as oxidized nicotinamide adenine dinucleotide is no longer recycled from reduced nicotinamide adenine dinucleotide via lactate dehydrogenase.[12] These high rates of glycolysis are uncoupled from the low rates of mitochondrial glucose oxidation during myocardial ischemia, which increases lactate and proton (H^+) accumulation and intracellular acidosis in the heart. The accumulation of H^+s represents an additional burden on the energy-starved, ischemic heart, as ATP is required to remove H^+s to alleviate the intracellular acidosis, which includes H^+ pumps and various transporters coupled to H^+ transport into the extracellular space, endoplasmic reticulum, or mitochondria.[10] Acidosis also attenuates the contractile function of the ischemic myocardium, as H^+s may desensitize the contractile filaments to Ca^{2+}, causing a further reduction in the contractility of the heart.[13] Because ATP is redirected away from supporting contractile function, while the contractile proteins themselves demonstrate a diminished contractile response, the uncoupling of glycolysis from glucose oxidation during myocardial ischemia results in a decline in cardiac/contractile efficiency.[10] Conversely, it has been argued that high glycolysis rates during ischemia may be protective, as time to onset of contracture during myocardial ischemia is very closely related to glycolytic ATP production.[14]

Energy metabolism in the reperfused myocardium

As sustained myocardial ischemia will lead to the death of cardiac myocytes and result in myocardial infarction, oxygen delivery to the ischemic myocardium must be re-established; this is primarily achieved via either primary percutaneous coronary intervention or thrombolytic therapies.[15] Importantly, the re-establishment of oxygen and nutrient supply to the myocardium leads to the recovery of oxidative phosphorylation and subsequent ATP production. Whereas both fatty acid and glucose oxidation recover during reperfusion, the reperfused myocardium is exposed to high levels of circulating fatty acids during the immediate stages of reperfusion due to the ischemic stress and ensuing sympathetic nervous system activation. These high levels of fatty acids are accompanied by an increase in myocardial fatty acid uptake and oxidation, which limits the initial recovery of glucose oxidation.[16,17] Whereas the "Randle Cycle" phenomenon contributes to this metabolic profile, at a molecular level, this is partly controlled by 5'AMP activated protein kinase (AMPK) activity. AMPK is activated during the preceding ischemia and lowers myocardial malonyl coenzyme A (CoA) levels, an endogenous inhibitor of mitochondrial fatty acid uptake through carnitine palmitoyltransferase-1 (CPT-1), thereby increasing fatty acid oxidation in the reperfused myocardium.[18] However, glycolysis rates remain high during the immediate stages of reperfusion, and thus uncoupling of glycolysis from glucose oxidation persists.[16] As such, lactate and H^+s continue to accumulate, and ATP must once again be diverted away from supporting contractile function towards re-establishing ionic homeostasis in the reperfused myocardium, which impairs cardiac efficiency, as alluded to in the previous section.

With the restoration of flow during reperfusion, the accumulating lactate and H^+s can now be washed out and removed from cardiac myocytes through the actions of the monocarboxylic acid transporters.[19] Furthermore, increased activity of the Na^+/H^+ exchanger can reduce the cytosolic H^+ load in exchange for Na^+, which causes an intracellular Na^+ overload. To reduce the Na^+ overload, the Na^+/Ca^{2+} exchanger can function in reverse mode, extruding Na^+ into the extracellular space while countertransporting Ca^{2+}.[20] However, this leads to an intracellular Ca^{2+} overload, which can limit contractile function of the reperfused myocardium by desensitizing contractile proteins to the stimulatory actions of Ca^{2+}. In addition, ATP must once again be diverted away from supporting contractile function during critical stages of cardiac recovery during reperfusion in order to correct ionic imbalances (eg, sarcoplasmic Ca^{2+} ATPase for clearing excess Ca^{2+} from the cytosol). Taken together, the metabolic perturbations that take place during successful reperfusion of the ischemic myocardium contribute to the deterioration of cardiac/contractile efficiency and thus may be a possible target for therapeutic intervention.

Cardiac energy metabolism as a target for myocardial ischemia and reperfusion

As the aforementioned metabolic perturbations during myocardial ischemia and reperfusion appear to play a critical role in the pathology of ischemic heart disease, the optimization of myocardial energy metabolism continues to be explored both in preclinical and clinical studies (*Figure 1*). One such approach is to stimulate glucose oxidation during ischemia and reperfusion, either directly or indirectly, by inhibiting myocardial fatty acid oxidation, which will increase glucose oxidation through the "Randle Cycle" effect. Glucose oxidation rates can be directly increased by using dichloroacetate (DCA) to stimulate the activity of pyruvate dehydrogenase (PDH), the rate-limiting enzyme of glucose oxidation.[21] DCA stimulates glucose oxidation by inhibiting PDH kinases, which phosphorylate PDH to inhibit its activity. Numerous preclinical studies have shown that in vivo treatment of either the isolated rodent heart or mouse with DCA, causes an improvement in the recovery of cardiac function during ischemia/reperfusion, while also reducing infarct size.[16,22] In nine subjects with coronary artery disease, intravenous infusion with DCA (35 mg/kg) resulted in an increased cardiac/contractile efficiency and left ventricular stroke volume.[23] Despite these promising findings, long-term clinical use with DCA is limited due to its very short half-life.[24]

Due to the previously mentioned "Randle Cycle" effect, glucose oxidation can also be stimulated secondary to the inhibition of fatty acid oxidation. Indeed, trimetazidine is a fatty acid oxidation inhibitor through an inhibition of 3-ketoacyl CoA thiolase[25,26] and has been shown to improve glucose oxidation rates and the recovery of cardiac function and efficiency after

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myocardial ischemia and reperfusion of isolated working rat hearts.[27,28] Trimetazidine is clinically approved for the treatment of angina pectoris in multiple countries in Asia, Europe, South America, Central America, Africa, and the Pacific Rim, where its use is often associated with reduced angina attacks and nitroglycerin usage, and also increased exercise duration, when given either as a monotherapy or in combination.[25,29]

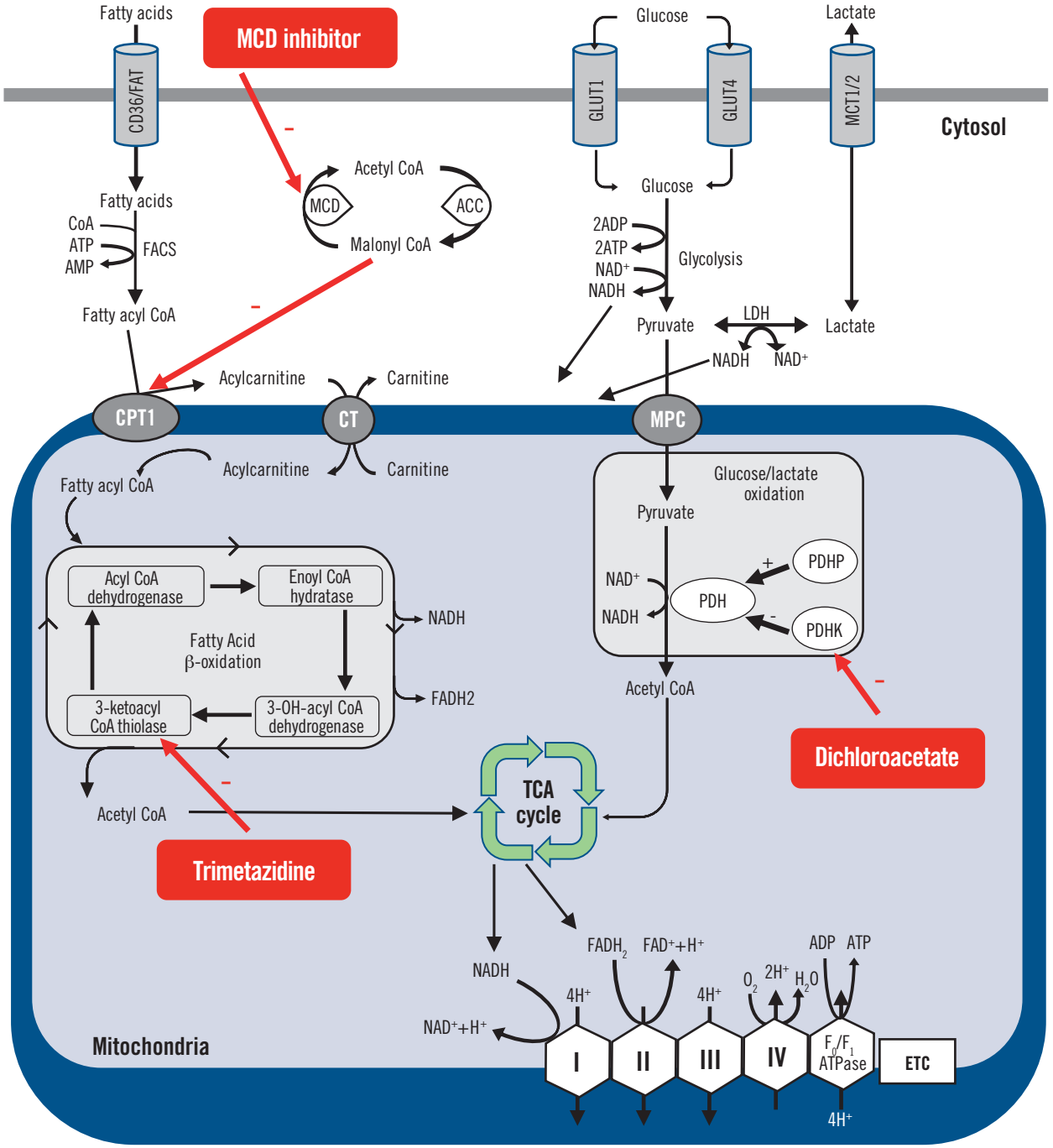

Figure 1 *Myocardial energy metabolism as a target for cardioprotection during myocardial ischemia and reperfusion. Illustration depicts the major metabolic pathways providing energy for the heart (eg, glycolysis, glucose oxidation, fatty acid oxidation) and various targets that can be modified to modulate myocardial energy metabolism in people with ischemic heart disease. Fatty acid oxidation can be targeted directly via inhibiting 3-ketoacyl CoA thiolase (trimetazidine), or indirectly via inhibiting CPT-1 to decrease mitochondrial fatty acid uptake (MCD inhibitors). With regards to glucose oxidation, pyruvate dehydrogenase (PDH) activity and subsequent glucose oxidation can be stimulated via inhibiting PDH kinase (dichloroacetate), which prevents inhibitory phosphorylation of PDH.*

ACC, acetyl coenzyme A (CoA) carboxylase; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CD36, cluster of differentiation 36; CPT-1, carnitine palmitoyltransferase 1; CT, carnitine translocase; ETC, electron transport chain; FACS, fatty acyl CoA synthase; FAD, flavin adenine dinucleotide; FAT, fatty acid translocase; GLUT, glucose transporter; LDH, lactate dehydrogenase; MCD, malonyl CoA decarboxylase; MCT, monocarboxylic acid transporter; MPC, mitochondrial pyruvate carrier; NAD, nicotinamide adenine dinucleotide; PDH, pyruvate dehydrogenase; PDHK, PDH kinase; PDHP, PDH phosphatase; TCA, tricarboxylic acid.

As mentioned previously, fatty acid oxidation can also be inhibited by malonyl CoA, which decreases mitochondrial fatty acid uptake via inhibiting CPT-1 activity. Preclinical studies have demonstrated that inhibiting the enzyme responsible for malonyl CoA degradation—malonyl CoA decarboxylase (MCD)—increases malonyl CoA levels, which results in an inhibition of fatty acid oxidation and subsequent elevation in glucose oxidation rates in isolated working rat hearts.[30] These metabolic alterations have been recapitulated in whole-body MCD-deficient mice,[31] and both pharmacological or genetic inhibition of MCD have been shown to improve the recovery of cardiac function and decrease infarct size in rodents subjected to myocardial ischemia and reperfusion.[22,30-32]

In opposition to these studies, stimulating AMPK activity, which lowers malonyl CoA levels and augments fatty acid oxidation rates, has also been shown to reduce infarct size in vivo and to improve functional recovery of isolated mouse hearts when subjected to myocardial ischemia and reperfusion.[33,34] Reasons for these discrepancies remain to be determined but could be due to AMPK also possessing antiapoptotic actions that could decrease death of cardiac myocytes during reperfusion-related injury.[35]

Conclusion

Taken together, accumulating evidence supports that alterations in energy metabolism contribute to myocardial ischemia and reperfusion-related cardiac dysfunction and clinical outcomes. Accordingly, strategies to correct these metabolic perturbations appear promising for the treatment of ischemic heart disease. A plethora of studies indicate that strategies to increase myocardial glucose oxidation are beneficial during myocardial ischemia and reperfusion, probably due to improved coupling between glycolysis and glucose oxidation, which limits myocardial acidosis and augments cardiac efficiency. Although there is ongoing debate surrounding the role of fatty acid oxidation as a target for ischemic heart disease, trimetazidine's success in angina patients provides support for inhibiting myocardial fatty acid oxidation in these individuals. Nonetheless, future preclinical and clinical studies are necessary to determine the ideal molecular target to modify energy metabolism, as well as the cellular mechanisms by which this approach improves cardiovascular outcomes in people with ischemic heart disease. ■

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