Optimizing cardiac energy substrate metabolism: a novel therapeutic intervention for ischemic heart disease

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Abstract

Ischemic heart diseases, encompassing and ranging from angina pectoris to acute myocardial infarction, have a major impact on both cardiac energy metabolism and cardiac function. In the normal heart, energy metabolism and function are exquisitely matched. However, during and after ischemia there are both a decrease in energy production and disturbances in the balance between use of fatty acid and of glucose by the heart. The dominance of fatty acid oxidation as a source for the generation of ATP at the expense of glucose oxidation during and after ischemia has a negative impact on both cardiac efficiency and cardiac contractile function. Thus optimizing energy substrate metabolism, such that the efficiency of both generating and utilizing ATP is maximized has emerged as a novel therapeutic intervention in various manifestations of ischemic heart disease. For example, the antianginal benefit of trimetazidine can be attributed to the partial inhibition of fatty acid oxidation and the reciprocal increase in glucose oxidation. This optimization of the balance between fatty acid and glucose metabolism results in an improvement in the efficiency of both the generation and utilization of ATP. Other pharmacological agents also exploit this plasticity and interdependence between the pathways of fatty acid and glucose oxidation. This is achieved either by altering flux through these metabolic pathways, or by altering the availability of circulating energy substrates. Thus the multitude of targets available to optimize myocardial energy metabolism may significantly increase the armamentarium of therapeutic interventions for preserving cardiac contractile function and limit the untoward effects of ischemic heart disease.

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Introduction

Alterations in myocardial energy substrate metabolism contribute significantly to ischemic heart disease. Angina pectoris is a common form of ischemic heart disease, and has an impact on both the amount of energy produced by the heart and the type of fuel it metabolizes. In this context, a growing body of evidence indicates that the modulation and optimizing of myocardial energy substrate metabolism are useful therapeutic interventions for the treatment of various forms of ischemic heart disease, including angina pectoris.

The heart is an omnivorous organ. It uses fatty acids, glucose, lactate, and ketone bodies as fuels to sustain contractile function. The contribution of each substrate to the overall production of ATP is tightly regulated, with each pathway possessing a considerable

degree of plasticity and interdependence. Under normal aerobic conditions, the heart relies primarily on fatty acids as substrates for oxidative metabolism. Fatty acid β-oxidation normally contributes 60–70% of total ATP production in the healthy adult heart; the remainder is provided mainly by carbohydrate oxidation (glucose oxidation and lactate oxidation), and also (at a very low percentage) by the oxidation of ketone bodies [1,2]. With respect to the major ATP-producing processes in the heart, fatty acid oxidation produces more ATP per molecule oxidized than does glucose oxidation; however, fatty acid oxidation requires a greater amount of oxygen per molecule of ATP produced. Thus fatty acid oxidation is less efficient than glucose oxidation with regards to ATP production per molecule of oxygen consumed.

Disease states and other conditions (eg, elective cardiac surgical procedures) that result in a serious insult to the heart can perturb the tightly regulated energetic balance in the heart, which can contribute to myocardial damage. An example of this is ischemic heart disease, which dramatically alters both the rate of energy production and the source of energy supply. During ischemia, oxygen availability is reduced as a result of deficient tissue perfusion, resulting in a mismatch between oxygen demand and oxygen supply. A decrease in oxygen supply results in a concomitant decline in the rates of mitochondrial oxidative metabolism. During ischemia, glycolysis becomes increasingly important because of its ability to generate ATP in the absence of oxygen. Unfortunately, this can lead to the intracellular accumulation of lactate and protons (H^+), which in itself can decrease cardiac efficiency. Furthermore, during ischemia, plasma free fatty acid concentrations increase dramatically, and result in the rapid recovery of fatty acid oxidation during subsequent reperfusion of the ischemic myocardium. These increased rates of fatty acid oxidation uncouple glycolysis and glucose oxidation, and so increase H^+ production. The dramatic increase in rates of fatty acid oxidation in early reperfusion can impair the recovery of cardiac function.

As knowledge of how cardiac energy metabolism is regulated increases, the potential application of metabolic modulation to the treatment of ischemic heart disease has become the subject of extensive research and review. The aim of this article is to present the mechanistic basis for the use of pharmacological agents to optimize myocardial energy substrate metabolism in order to limit the deleterious consequences of ischemia.

Myocardial energy metabolism

Under aerobic conditions, more than 50% of the ATP produced in the heart is derived from mitochondrial oxidative phosphorylation (*Figure 1*) [1,2]. Reducing equivalents (H^+ and electrons) are transferred from substrates to the mitochondria by the reduced forms of flavine adenine dinucleotide ($FADH_2$) and nicotinamide adenine dinucleotide (NADH), generated by dehydrogenase reactions occurring during β-oxidation, the Krebs (tricarboxylic acid [TCA]) cycle and pyruvate oxidation (glucose oxidation). The extents to which the various metabolic pathways contribute to the production of ATP are dependent on energetic demand, which itself is determined by contractile work.

In the presence of a normal oxygen supply, glucose and fatty acids both undergo oxidation through different processes that link at the level of the TCA cycle

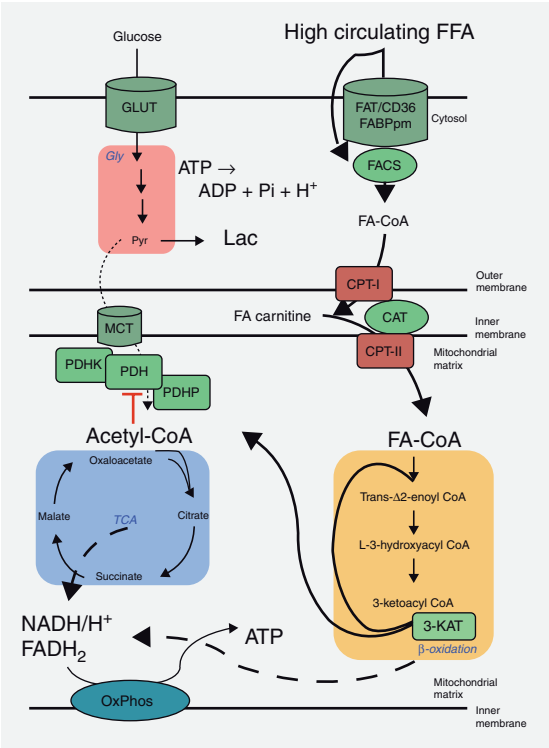

Figure 1. Glucose/fatty acid cycle. In the presence of high concentrations of circulating free fatty acids, fatty acid uptake and oxidation increase considerably, resulting in an accumulation of acetyl coenzyme A (CoA), which in turn inhibits the pyruvate dehydrogenase (PDH) complex, uncoupling glycolysis from subsequent oxidation. This further results in the hydrolysis of glycolytic ATP uncoupled from oxidative metabolism and concomitantly increased production of cytosolic protons, which can result in intracellular acidosis. CAT, carnitine acyl translocase; CPT, carnitine palmitoyl transferase; FABPpm, fatty acid binding protein of the plasma membrane; FACS, fatty acyl CoA synthase; FA CoA, fatty acyl CoA; FAT/CD36, fatty acid transporter; FFA, free fatty acid; GLUT, glucose transporter; Gly, glycolysis; 3-KAT, 3-ketoacyl CoA thiolase; Lac, lactate; MCT, monocarboxylic transporter; OxPhos, oxidative phosphorylation; PDHK, pyruvate dehydrogenase kinase; PDHP, pyruvate dehydrogenase phosphatase; Pi, inorganic phosphate; Pyr, pyruvate; TCA, tricarboxylic acid cycle.

(*Figure 1*). The presence of this common pathway is central both to the mechanisms regulating flux through these pathways and to the interdependence of these processes for ATP production.

Glucose used for the generation of ATP originates from the blood stream, or is liberated from endogenous glucose stores (ie, glycogen). Glucose enters the cardiac myocyte via glucose transporters (GLUTs) [3]. GLUT 4 is the main myocardial glucose transporter, and is sensitive to insulin stimulation, whereas a small percentage of glucose transport occurs via the insulin-insensitive transporter, GLUT 1. By the glycolytic pathway, glucose is converted into pyruvate with the net production of two molecules of ATP and two molecules of NADH. In the presence of oxygen, pyruvate is oxidized (glucose oxidation) by the pyruvate dehydrogenase (PDH) complex to form acetyl coenzyme A (CoA), which then feeds into the TCA cycle. Alternatively, in the absence of adequate oxygen, pyruvate can be converted to lactate by the enzyme lactate dehydrogenase (LDH), to regenerate the NAD^+ required to maintain glycolysis. The PDH complex is rate-limiting for glucose oxidation, and is highly sensitive to product inhibition by acetyl CoA. When high rates of fatty acid oxidation are present, there is an increase in the concentration of acetyl CoA, which in turn can inhibit glucose oxidation [4–6]. This reciprocal inter-regulatory relationship between glucose oxidation and fatty acid oxidation was originally described by Philip Randle, and is known as the glucose/fatty acid cycle or Randle cycle [7].

On the other side of oxidative metabolism lies fatty acid oxidation. Fatty acid oxidation occurs mainly in the mitochondrial matrix and is highly dependent on the delivery of fatty acids, first from the plasma to the cytoplasm, and subsequently from the cytoplasm to the mitochondrial matrix. Fatty acids enter the cardiac myocyte either by passive diffusion or via protein-mediated uptake. The key transporters involved in fatty acid uptake are fatty acyl translocase (FAT/CD36) and the plasma membrane isoform of fatty acid binding protein (FABPpm) [3,8]. Fatty acids are then esterified to fatty acyl CoA, which is mediated by a family of fatty acyl CoA synthase (FACS) enzymes. The mitochondrial uptake of fatty acyl CoAs is mediated by carnitine palmitoyl transferases (CPT) I and II and carnitine acyl translocase (CAT) [1,9]. CPT-I is present on the outer mitochondrial membrane. It binds to fatty acyl CoAs and catalyzes the formation of fatty acyl carnitines which are transported to the mitochondrial inter-membrane space. There, CAT translocates fatty acyl carnitines into the matrix (in exchange for carnitine), where CPT-II re-esterifies acyl carnitines into acyl CoAs (*Figure 1*). Matrix acyl CoAs can then be progressively metabolized by fatty acid oxidation. Four main enzyme classes are involved in the mitochondrial fatty acid oxidation: acyl CoA dehydrogenase, 2-enoyl CoA hydratase, 3-hydroxyacyl CoA dehydrogenase and 3-ketoacyl CoA thiolase (3-KAT). In the fatty acid oxidation spiral, fatty acyl CoAs are broken down to acetyl CoA, which feeds into the TCA cycle for the production of ATP. Both acyl CoA dehydrogenase and 3-hydroxyacyl CoA dehydrogenase are sensitive to the redox state of the matrix (FAD/$FADH_2$ and NAD^+/NADH ratios). In the presence of high rates of glucose oxidation, the concentration of NADH is increased, and the redox state of the mitochondria favors an inhibition of fatty acid oxidation. Fatty acid oxidation is also regulated at the level of 3-KAT, which is sensitive to the acetyl CoA/CoA ratio, and in the presence of high glucose oxidation rates acetyl CoA accumulates and inhibits 3-KAT.

On the basis of the enzymes involved in fatty acid oxidation, there are numerous targets available that can be exploited to optimize and modulate myocardial energy metabolism in order to limit the untoward effects of ischemic heart disease. Several pharmacological approaches to the optimization of energy substrate metabolism at the level of the balance between fatty acid and glucose metabolism (*Figure 2*) are considered below.

Carnitine palmitoyl transferase I inhibitors

Carnitine palmitoyl transferase-I is considered to be the rate-limiting enzyme for mitochondrial uptake of fatty acids. As a result, pharmacological agents exerting their anti-ischemic effects by inhibiting CPT-I have potential for therapeutic use in the treatment of ischemic heart disease (*Figure 2*). CPT-I inhibitors that have been developed for this purpose include oxfenicine, etomoxir, and perhexiline. Several experimental studies have demonstrated that the protective effects of oxfenicine [10,11], etomoxir [12,13], and perhexiline [11,14] are associated with a shift in energy substrate metabolism from fatty acid oxidation towards glucose oxidation. Of these compounds, perhexiline has received the most clinical attention.

Perhexiline was frequently prescribed as an anti-anginal agent in the 1970s; however, its use declined in the 1980s because of adverse effects, including hepatic toxicity (steatosis and necrosis), and peripheral neuropathy [15]. The mechanism responsible for these adverse effects of perhexiline is believed to be accumulation of phospholipid, secondary to the inhibition of CPT-I, and these adverse effects can therefore be presumed to be shared by CPT-I inhibitors as a class of drugs. It is of importance to note that the hepatotoxic effects of perhexiline arise as a result of the inhibition of hepatic CPT-I [16]; however, in-vitro studies indicate that the cardiac isoform of CPT-I is more sensitive to inhibition by perhexiline than is the hepatic CPT-I isoform [17]. Furthermore, monitoring

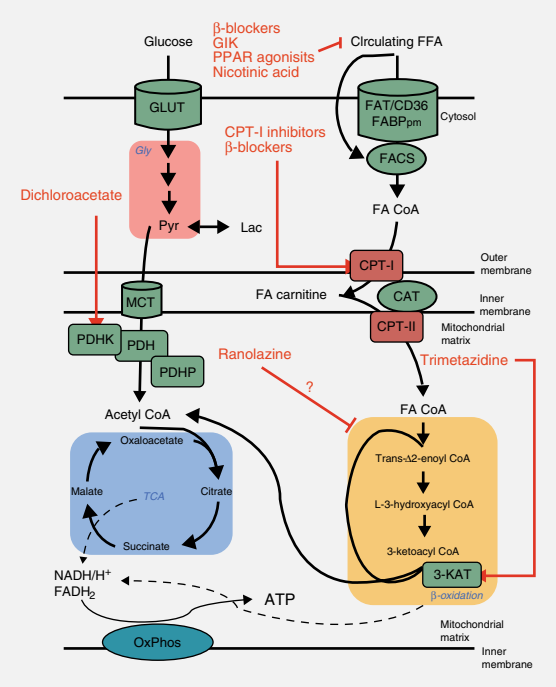

Figure 2. Pharmacological optimization of fatty acid and glucose metabolism. Three major metabolic pathways provide the necessary energy for heart function: fatty acid β-oxidation, glycolysis (Gly), and glucose oxidation (glycolysis + pyruvate [Pyr] oxidation by the tricarboxylic acid [TCA] cycle). Pharmacological compounds (shown in red) can modify energy substrate metabolism by modulating circulating concentrations of free fatty acids (FFA) and enzymatic activity at the levels of glucose oxidation, carnitine palmitoyl transferase (CPT)-I, and fatty acid oxidation. CAT, carnitine acyl translocase; CoA, coenzyme A; FABPpm, fatty acid binding protein of the plasma membrane; FA CoA, fatty acyl CoA; FACS, fatty acyl CoA synthase; FAT/CD36, fatty acid transporter; FFA, free fatty acid; GLUT, glucose transporter; Gly, glycolysis; 3-KAT, 3-ketoacyl CoA thiolase; Lac, lactate; MCT, monocarboxylic transporter; OxPhos, oxidative phosphorylation; PDH, pyruvate dehydrogenase (complex); PDHK, pyruvate dehydrogenase kinase; PDHP, pyruvate dehydrogenase phosphatase.

the plasma concentration of perhexiline and maintaining it in the therapeutic range of 150–600 μg/L markedly limits the serious adverse effects of the drug while preserving its anti-ischemic efficacy [18]. Accordingly, the potential of targeting myocardial energy substrate metabolism to limit the consequences of ischemia has led to a resurgence in the use of perhexiline.

With the biochemical mechanisms responsible for both its therapeutic and its adverse effects being elucidated, perhexiline is used as antianginal agent in New Zealand, Australia, and most European countries, on a named-patient basis. Furthermore, clinical trials have demonstrated the utility of perhexiline in refractory angina pectoris [18], aortic stenosis [19], and chronic heart failure (of ischemic and non ischemic origin) [20], in which it improves symptomatic status, left ventricular ejection fraction, and quality of life. Therefore, inhibition of CPT-I and fatty acid oxidation, with the resultant reciprocal increase in glucose oxidation, is a cardioprotective strategy that is effectively utilized in diverse forms of ischemic heart disease.

β-Adrenoceptor antagonists and myocardial energy substrate metabolism

The anti-ischemic properties of β-adrenoceptor antagonists (β-blockers) are classically attributed to an oxygen-sparing effect elicited by negative inotropic and chronotropic actions. In addition to effects on cardiac contractility, β-blockers also possess additional anti-ischemic mechanisms related to energy substrate metabolism. They reduce neurohormonal activation, and thereby can reduce catecholamine-induced lipolysis, and hence circulating plasma fatty acid concentrations (*Figure 2*) – a major determinant of the rates of fatty acid oxidation. Furthermore, several clinical studies have indicated that β-blockers decrease fatty acid uptake [21,22] and increase left ventricular function, independently of decreased oxygen consumption [23,24] – effects indicative of increased cardiac efficiency (work/oxygen consumed). These effects are probably related to the ability of β-blockers to inhibit the activity of CPT-I (*Figure 2*) [25], and induce a shift in energy substrate metabolism from fatty acid oxidation towards glucose oxidation [26].

3-Ketoacyl-coenzyme A thiolase inhibitors

Being a key enzyme in fatty acid oxidation, 3-KAT has emerged as a target for modifying fatty acid oxidation. Trimetazidine is the first of a class of partial fatty acid oxidation inhibitors that competitively inhibit the terminal enzyme of fatty acid oxidation, long-chain 3-ketoacyl CoA thiolase (*Figure 2*) [27,28]. It is clinically utilized as an antianginal agent throughout Europe and more than 90 countries worldwide [29]. The protective effects of trimetazidine are demonstrable in experimental models of ischemia-reperfusion. It decreases ischemic contracture, and lessens the increase in diastolic pressure during reperfusion after ischemia [30], and inhibits cardiac myocyte apoptosis to preserve cardiac function during reperfusion [31]. With regards to the mechanism of its anti-ischemic action, trimetazidine also protects hearts from the deleterious effects of fatty acids on the recovery of cardiac function [32]. By virtue of inhibiting fatty acid oxidation, it reciprocally stimulates glucose oxidation [27,28], and thus improves the

coupling between glycolysis and glucose oxidation, thereby decreasing the rate of H^+ production attributable to the hydrolysis of glycolytically derived ATP. These effects of trimetazidine on the pathways of fatty acid and glucose metabolism can prevent deleterious alterations in intracellular ionic homeostasis by diminishing the potential for intracellular acidosis during ischemia, in addition to intracellular Na^+ and Ca^{2+} overload during reperfusion [33,34]. Therefore, the metabolic effects of trimetazidine increase cardiac efficiency by sparing ATP hydrolysis from being utilized for correcting ionic homeostasis, thus increasing the amount of ATP hydrolysis available to drive meaningful contractile work.

Numerous clinical trials have demonstrated the efficacy of trimetazidine in various forms of ischemic heart disease, ranging from angina pectoris to acute myocardial infarction, ischemic cardiomyopathy, and heart failure. With respect to angina, the beneficial effects of trimetazidine include an increased time to 1 mm ST-segment depression, a reduction in weekly consumption of nitrates, and a reduction in the number of weekly angina attacks both in patients who have not undergone revascularization and in those undergoing revascularization via coronary artery bypass grafting procedures or percutaneous coronary intervention [35]. Trimetazidine also has cardioprotective effects in the setting of acute myocardial infarction, where it reduces reperfusion arrhythmias [36] and reduces the time to resolution of ST-segment elevation [37]. Furthermore, trimetazidine added to existing treatment has been shown to improve New York Heart Association (NYHA) functional class, decrease left ventricular end-systolic volume, and increase left ventricular ejection fraction in patients with ischemic cardiomyopathy and heart failure [38,39]. Therefore, the partial inhibition of fatty acid β-oxidation with trimetazidine limits the deleterious consequences of myocardial ischemia in varied manifestations of ischemic heart disease.

Ranolazine, similar to trimetazidine, is a partial inhibitor of fatty acid oxidation, although the molecular target responsible for this effect remains to be identified (*Figure 2*). It is now approved for use as an antianginal agent in the USA [40], and, in addition to its metabolic effects, appears to have antiarrhythmic activity. Experimental studies have demonstrated that ranolazine preserves mitochondrial ultrastructure, decreases tissue Ca^{2+} content, and improves the recovery of ventricular function during reperfusion after ischemia [41], in addition to decreasing the incidence of ventricular fibrillation during reperfusion [42]. It has also been reported to reduce the magnitude of myocardial stunning [43] and to reduce infarct size [44]. Furthermore, in canine models of heart failure, ranolazine improves ejection fraction and stroke volume without increasing oxygen consumption, and hence increases myocardial efficiency [45,46].

Several of the beneficial actions of ranolazine are most probably attributable to either a greater amount of ATP synthesized at a given level of oxygen consumption or a more effective use of the energy released from ATP hydrolysis – effects that can be explained by a shifting of myocardial energy substrate preference from fatty acid oxidation to glucose oxidation (described above) [47–49].

Clinical trials have demonstrated the antianginal efficacy of ranolazine. Both as monotherapy and in combination therapy with standard antianginal regimens, it has been shown to increase exercise duration, increase time to 1 mm ST-segment depression, reduce the weekly number of angina attacks, and reduce weekly consumption of nitroglyerin [50–53]. Furthermore, the antianginal efficacy of ranolazine is similar in both non diabetic and diabetic patients [54].

Recent clinical trials have also indicated that ranolazine decreases the incidence of ventricular tachycardia, supraventricular tachycardia, and ventricular pauses, and has no adverse effect on survival, thus confirming its long-term safety and efficacy [55,56]. The antiarrhythmic effects of the drug may be attributable to its effects on various cardiac ionic currents, particularly the late Na^+ current (for review see [57]). Interestingly, the antianginal and antiarrhythmic effects of ranolazine occur at similar therapeutic concentrations (10–20 μmol/L), and thus are probably not mutually exclusive. The effects on ranolazine on the pathways of fatty acid and glucose oxidation probably underlie its antianginal activity by improving the efficiency of ATP production.

Dichloroacetate

Dichloroacetate, like trimetazidine and ranolazine, also facilitates the shift in the balance of myocardial energy substrate metabolism away from fatty acid oxidation towards glucose oxidation; however, unlike trimetazidine and ranolazine, dichloroacetate exerts direct effects on the mitochondrial PDH complex. It inhibits the activity of PDH kinase, and thus stimulates glucose oxidation (*Figure 2*). Experimental studies have demonstrated the efficacy of dichloroacetate in enhancing the recovery of cardiac function during reperfusion after ischemia both in vitro and in vivo [58–60]. The protective effects of dichloroacetate are accompanied by a stimulation of the rate of glucose oxidation, and a resultant improved coupling between glycolysis and glucose oxidation (which reduces the production of H^+ attributable to glucose metabolism), and an increase in myocardial efficiency (work per molecule of oxygen consumed) [61,62].

Although clinical experience with dichloroacetate is limited, its metabolic mechanism of action appears to persist in the setting of heart failure. In a small clinical trial, dichloroacetate increased left ventricular stroke volume and myocardial efficiency, effects accompanied by increased utilization of lactate [63], which itself is probably the result of an increased rate of pyruvate oxidation (ie, glucose oxidation). These metabolic effects of dichloroacetate may be of therapeutic relevance in angina pectoris; however, they remain to be assessed in this setting.

Glucose–insulin–potassium for acute coronary syndromes

The concept of using glucose–insulin–potassium (GIK) solutions to protect the ischemic myocardium in acute coronary syndromes encompassing clinical conditions ranging from myocardial infarction to unstable angina was initially introduced by Sodi-Pollares et al [64]. The beneficial effects of GIK on cardiac energy metabolism that underlie the protection it affords were originally proposed by L.H. Opie as promotion of glycolysis and reduction in circulating fatty acids (*Figure 2*), with a resultant decrease in cardiac fatty acid metabolism [65]. Indeed, experimental studies have demonstrated the ability of GIK to suppress circulating fatty acid concentrations, while maintaining circulating glucose concentration [66]. These effects on circulating energy substrate concentrations are effective in inducing a shift in myocardial substrate preference from fatty acid to glucose utilization [67], and in improving post-ischemic recovery of contractile function, reducing the release of creatine kinase and lactate dehydrogenase, and reducing infarct size [66,67]. However, the protective effects of GIK are not unambiguous, as previous reports also indicate a lack of reduction in infarct size [68]. This ambiguity of GIK in experimental studies may be related to the complex nature of its effects on myocardial energy substrate metabolism – specifically, its ability to accelerate the rate of glycolysis disproportionately to that of glucose oxidation, and thus to increase the rate of H^+ production attributable to myocardial glucose metabolism, which can impair postischemic recovery of function [69].

The ambiguous effects of GIK on myocardial protection are transferred to the clinical setting, where GIK has been shown to be beneficial, neutral, and detrimental. A meta-analysis of GIK in the 'prethrombolytic' era demonstrated the ability of GIK to reduce the mortality associated with acute myocardial infarction [70], which was also evident in the thrombolytic era, as demonstrated by the Diabetic Patients with Acute Myocardial Infarction (DIGAMI) study [71] and the Estudios Cardiologicos Latinoamerica (ECLA) Collaborative Group [72]. However, a Polish GIK study (Pol-GIK) failed to demonstrate any benefit of GIK on cardiovascular mortality [73]. Furthermore, in contrast to the Dutch Glucose–Insulin–Potassium Study 1 (GIPS 1), which demonstrated a survival benefit of GIK in a subset of patients [74], the Dutch GIPS 2 study, which assessed the effects of GIK on mortality and infarct size had to be stopped early because of a potentially greater mortality in the GIK group [75]. These differences in clinical outcomes may be related to the differing doses used, the timing of administration, and the functional NYHA classes of the patient populations. As there remains no clear consensus with regards to the beneficial, neutral, or detrimental clinical effects of GIK in acute coronary syndromes, further study is warranted.

Peroxisome proliferator-activated receptor agonists

Peroxisome proliferator-activated receptors (PPARs) are members of the ligand-activated nuclear hormone receptor superfamily. PPARs exert major influences on lipid metabolism at the whole-body level (*Figure 2*); specifically, they have a central role in regulating the balance between fatty acid oxidation and fatty acid storage, by regulating the expression of enzymes involved in both fatty acid oxidation and lipogenesis [76]. Three distinct PPAR isoforms, with overlapping yet differing/preferential tissue distributions, have been identified in mammals: PPARα, PPARγ, and PPARδ. Expression of PPARα is greatest in tissues with a high capacity for fatty acid oxidation, including the liver, skeletal muscle, and heart [76,77]. PPARγ is expressed to the greatest extent in adipose tissue, with only low concentrations detected in the skeletal and cardiac muscle. PPARδ is the predominant isoform expressed in skeletal muscle, white adipose tissue, and brown adipose tissue (in rodents) [78]. Importantly, PPARs are the molecular targets of several clinically useful pharmacological agents that alter whole-body lipid metabolism.

PPARα is the molecular target of the antihyperlipidemic fibrate class of drugs (clofibrate, fenobibrate, gemfibrozil). Fibrates differentially affect the fatty acid binding capacity of cytosolic proteins from different tissues. They increase the fatty acid binding capacity of liver and kidney while not affecting that of skeletal muscle and decreasing that of cardiac cytosolic proteins [79]. This may be associated with the ability of fibrates to increase the expression and activity of long-chain acyl CoA synthetase in extracardiac tissue [80]. Furthermore, fibrates have been shown to increase the expression of the enzymes involved in fatty acid

oxidation preferentially in the liver [81]. Taken together, these effects increase extracardiac fatty acid utilization, decreasing both circulating plasma and myocardial fatty acid concentrations, and thus myocardial fatty acid oxidation. Experimental studies have demonstrated that fibrates can improve the recovery of cardiac function after ischemia [82], and reduce infarct size [83] – protective effects that may arise as a result of the partitioning of fatty acids away from the heart.

PPARγ is the molecular target of the oral antidiabetic thiazolidinedione class of drugs (rosiglitazone, pioglitazone, troglitazone). Thiazolidinediones prevent the spillover of lipids from adipose tissue into non adipocytes (eg, cardiac myocytes), thereby increasing adiposity, an effect attributed to a reduction in the ectopic deposition of fatty acids in tissues not suited for the storage of excess lipid. Experimental studies have demonstrated that thiazolidinediones can decrease circulating plasma triglyceride [84] and fatty acid [84,85] concentrations, while increasing both myocardial glucose uptake [86] and net lactate uptake [85] (indicative of increased glucose oxidation) and glucose oxidation [84]. These alterations in energy substrate selection and metabolism translate into improvements in the recovery of cardiac function after ischemia [84,85,87].

Interestingly, there exists discordance between the protective effects of thiazolidinediones in experimental studies and the potential to exacerbate the symptoms of heart failure in some diabetic patients treated with these compounds. Specifically, thiazolidinediones can cause fluid retention and peripheral edema, effects that are of concern in patients with heart failure [88]. Furthermore, the findings of a recent meta-analysis indicated that the use of thiazolidinediones in patients with type 2 diabetes mellitus is associated with an increase in the risk of myocardial infarction and an increased risk of death from cardiovascular causes [89]. Therefore, despite the potentially beneficial effects of thiazolidinediones on circulating plasma fatty acid concentrations and cardiac fatty acid and glucose metabolism, the use of thiazolidinediones in any cardiovascular disease state requires additional research and trials of safety.

PPARδ is not as well characterized as PPARα and PPARγ; however, experimental studies do implicate it in the regulation of fatty acid metabolism in skeletal muscle and adipose tissue. The activation of PPARδ in both skeletal muscle [90] and adipose tissue [91] increases fatty acid β-oxidation, and thus has the potential to reduce the circulating concentration of free fatty acids to which the heart is exposed, and thereby decreases cardiac fatty acid oxidation, which has protective effects in cardiac ischemia.

Nicotinic acid

Nicotinic acid is a broad-spectrum lipid-modifying agent that possesses antiatherogenic properties, including the ability to decrease the circulating concentrations of very-low density lipoproteins and low-density lipoproteins while increasing those of high-density lipoproteins. With regards to ischemic heart disease, nicotinic acid (both as monotherapy and in combination with other lipid-decreasing drugs) has been shown to decrease the progression of atherosclerotic lesions, and to increase plaque regression [92], effects shown to decrease cardiovascular mortality (for review see [93]). In addition to its antiatherogenic properties, nicotinic acid also has the ability to modify energy substrate metabolism.

A high-affinity G-protein-coupled receptor for nicotinic acid is highly expressed in adipose tissue [94] and is most probably responsible for the unique distribution of nicotinic acid to this tissue after administration. Nicotinic acid inhibits adipose tissue lipolysis and thus decreases circulating fatty acid concentrations (*Figure 2*). These effects alter both whole-body and cardiac energy metabolism by reducing the availability of fatty acids to peripheral tissues (eg, skeletal and cardiac muscle). Human studies have demonstrated that nicotinic acid increases the cardiac respiratory quotient while not affecting the oxygen extraction ratio – effects indicative of a shift in myocardial energy substrate preference from fatty acid to carbohydrate [95,96], which may contribute to potential anti-ischemic properties in the myocardium.

Summary

The modulation of myocardial energy substrate metabolism, particularly by shifting energy substrate preference from the use of fatty acids towards the use of glucose as an oxidative fuel, is a novel therapeutic intervention, not only for angina, but also for various other manifestations of ischemic heart disease. The shift in energy substrate preference can be achieved through the use of pharmacological agents that act at several levels of the pathways of fatty acid and glucose metabolism, altering the balance and contribution of these pathways to overall cardiac energetics and thereby increasing the efficiency of both the production and utilization of ATP. Such effects can be attained by regulating the rates of flux through the pathways of fatty acid oxidation and glucose oxidation, both by manipulating the activities of key enzymes and by altering the availability of circulating substrates. The efficacy of, for example, trimetazidine in the widespread treatment of angina is of particular relevance to the feasibility of modulating and optimizing energy substrate metabolism to limit

cardiac dysfunction in the setting of ischemic heart disease. ■

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