Glucose metabolism and cardiac hypertrophy

Stephen C. Kolwicz Jr and Rong Tian*

Mitochondria and Metabolism Center, Department of Anesthesiology and Pain Medicine, University of Washington School of Medicine, 815 Mercer Street, Seattle, WA 98109, USA

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Abstract

The most notable change in the metabolic profile of hypertrophied hearts is an increased reliance on glucose with an overall reduced oxidative metabolism, i.e. a reappearance of the foetal metabolic pattern. In animal models, this change is attributed to the down-regulation of the transcriptional cascades promoting gene expression for fatty acid oxidation and mitochondrial oxidative phosphorylation in adult hearts. Impaired myocardial energetics in cardiac hypertrophy also triggers AMP-activated protein kinase (AMPK), leading to increased glucose uptake and glycolysis. Aside from increased reliance on glucose as an energy source, changes in other glucose metabolism pathways, e.g. the pentose phosphate pathway, the glucosamine biosynthesis pathway, and anaplerosis, are also noted in the hypertrophied hearts. Studies using transgenic mouse models and pharmacological compounds to mimic or counter the switch of substrate preference in cardiac hypertrophy have demonstrated that increased glucose metabolism in adult heart is not harmful and can be beneficial when it provides sufficient fuel for oxidative metabolism. However, improvement in the oxidative capacity and efficiency rather than the selection of the substrate is likely the ultimate goal for metabolic therapies.

Keywords: Glycolysis • Metabolic flexibility • Foetal metabolic profile

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1. Introduction

Glucose is an important fuel that is used by nearly all organisms through a common set of metabolic pathways. Our knowledge of glucose metabolism dates back to 1860 with the identification of glycolysis by Louis Pasteur and climaxes in 1937 when the complete glycolytic pathway was unearthed through the work of Gustav Embden and Otto Fritz Meyerhof.1 In the same year, building on the work of Albert Szent-Gyorgyi, Hans A. Krebs and William A. Johnson showed that pyruvate could form succinate in animal tissues, thus providing the foundation for the citric acid cycle.2 More than 20 years later, Peter D. Mitchell hypothesized a chemiosmotic mechanism that ultimately led to the elucidation of the electron transport chain and oxidative phosphorylation,3 and thus, completed the pathway for aerobic glucose metabolism for ATP generation.

We now know that glucose can be metabolized in multiple pathways providing not only an energy supply, but also many other important metabolites for cell growth and function. Figure 1 provides an overview of the metabolic fates of glucose in a cardiac myocyte. Glucose enters the cardiac myocyte by facilitated diffusion via glucose transporters (GLUT). GLUT1 and GLUT4 are the major isoforms present in the heart; GLUT1 mediates insulin-independent and GLUT4 mediates insulin-sensitive glucose transport. Intracellular glucose is phosphorylated by hexokinase to glucose-6-phosphate (G-6-P) and through glycolysis eventually yields pyruvate, which is oxidized in the mitochondria. Although the amount of ATP derived from glycolysis is rather small (2ATP/glucose), it has been proposed to play a critical role for the maintenance of ion pump function due to the proximity of glycolytic enzymes and the ATPases.4,5 However, G-6-P can also be processed in several other pathways such as glycogen synthesis, the pentose phosphate pathway (PPP), or the aldose reductase (AR)/polyol pathway. Although glycolysis and pyruvate oxidation are the preferred fates of glucose, the accessory pathways play important roles in regulating biological functions of the cell.

2. Glucose metabolism is increased in cardiac hypertrophy

In the normal, adult heart, oxidation of fatty acids contributes the majority of carbon substrates to ATP generation.6 However, the heart possesses tremendous metabolic flexibility highlighted by its ability to utilize glucose, lactate, ketones, and amino acids. Preference in substrate utilization can change in response to altered substrate

* Corresponding author. Tel: +1 206 543 8982; fax: +1 206 616 4819, Email: rongtian@u.washington.edu

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availability or altered regulation of metabolic pathways. For example, it is well documented that fuel preference switches from glucose and lactate (collectively referred to as carbohydrates) in the foetal heart to predominantly lipids in the adult heart.\(^7,8\) It has also been observed that the substrate metabolism in animal models of cardiac hypertrophy recapitulates the ‘foetal metabolic profile’ with an increased preference for carbohydrate sources.\(^9 – 11\) This observation was consistent with the reappearance of the foetal gene expression in cardiac hypertrophy and was thus considered integral to the pathological remodelling of the heart. Although there are multiple cell types in the heart, this paper reviews the changes of myocardial energy metabolism in the beating heart which primarily originates from cardiomyocytes as they are responsible for the majority of oxygen consumption during contraction.\(^12\)

Major changes of glucose metabolism in cardiac hypertrophy are summarized in Figure 2. The hallmark of increased glucose metabolism in the hypertrophied heart is accelerated glycolysis, a finding supported by studies using carbon isotope labelling techniques in isolated perfused hearts.\(^13 – 16\) Consistent with this observation, several studies showed a higher rate of glucose uptake in animal models of cardiac hypertrophy.\(^16 – 19\) Interestingly, alterations in expression or capacity of glycolytic enzymes do not consistently coincide with increased glycolysis\(^16,18,20\) suggesting that the altered glycolytic flux is attributable to altered regulation rather than the expression of the glycolytic enzymes. Under aerobic conditions, NADH produced from glycolysis is delivered to the mitochondria through the malate–aspartate shuttle.\(^21\)

Pyruvate has the ability to participate in accessory pathways that supply carbon-based substrates to the tricarboxylic acid (TCA) cycle, a process termed ‘anaplerosis’.\(^35\) In particular, pyruvate can be carboxylated by pyruvate carboxylase yielding oxaloacetate or carboxylated by malic enzyme (ME) yielding malate. In hypertrophied rat hearts, an 80–90% increase in anaplerotic flux was observed and supported with increased tissue content of malate.\(^36,37\) A significant increase in the gene expression of ME without a change in pyruvate carboxylase\(^37\) supported the idea of increased anaplerosis through
the pyruvate–malate pathway. Although the increased anaplerotic flux in hypertrophied myocardium is sufficient to maintain overall TCA cycle flux, it reduces the efficiency of ATP production from pyruvate. To date, there is limited research on the contribution of anaplerosis in cardiac hypertrophy and its progression to heart failure. Further investigation in this direction is clearly warranted.

3. Potential mechanisms for increased glucose reliance

A large number of studies in the past two decades have demonstrated that the transcriptional regulation of genes involved in mitochondrial oxidative metabolism has changed significantly during the development of pathological hypertrophy and heart failure.\(^\text{38}\) Down-regulation of peroxisome proliferator-activated receptor alpha (PPAR\(\alpha\)) and peroxisome proliferator-activated receptor gamma co-activator-1 (PGC-1), master regulators of genes involved in fatty acid oxidation and mitochondrial biogenesis, has been observed in rodent models of cardiac hypertrophy and failure.\(^\text{32,39–42}\) The PPAR\(\alpha\) target, carnitine-palmitoyl transferase 1 (CPT1), which facilitates fatty acid transport into the mitochondria, is also down-regulated.\(^\text{18,37,41,43}\) Likewise, medium chain acyl-CoA dehydrogenase, an enzyme important for beta-oxidation, is also reduced.\(^\text{18,32,41}\) Moreover, it has been shown that the liver isoform of CPT1, which is highly expressed in the foetal heart, increases in pressure-overload hypertrophy.\(^\text{37}\) In addition, decreases in plasma membrane-bound fatty acid transporters\(^\text{44,45}\) and carnitine, which is necessary for transport of fatty acyl CoAs into the mitochondria,\(^\text{13,46,47}\) have been noted. Therefore, an overall reduction in the supply of cytosolic and mitochondrial fatty acids may be responsible for hampered fatty acid metabolism in cardiac hypertrophy. Deletion of PPAR\(\alpha\) in mice results in decreased FAO and increased glucose oxidation in the heart, whereas deletion of PGC-1\(\alpha\) and/or \(\beta\) results in decreased expression of proteins in oxidative phosphorylation, increased expression of foetal metabolic genes, and defective ATP supply.\(^\text{48,49}\) Therefore, it has been proposed that increased reliance on glucose is likely a counter to the down-regulation of FAO and overall oxidative metabolism in cardiac hypertrophy.

As described above, increased glycolytic flux in cardiac hypertrophy is associated with a higher rate of insulin-independent glucose uptake with no significant changes in the expression of the glucose transporter proteins or glycolytic enzymes.\(^\text{11,16,20,50}\) One of the mechanisms proposed for these findings is the activation of an intracellular energy-sensor, \(\delta\)-AMP-activated protein kinase (AMPK), triggered by impaired myocardial energetics.\(^\text{16,18,51}\) Increased AMPK activity promotes the translocation of the glucose transporters onto the plasma membrane and enhances glucose uptake.\(^\text{16}\) In addition, AMPK stimulates glycolysis by phosphorylation and activation of phosphofructokinase 2 (PFK2), which generates fructose-2,6-diphosphate that acts as a potent allosteric stimulant of the rate-limiting enzyme, PFK1.\(^\text{52,53}\) The AMPK mechanism is consistent with the observation that increased glucose uptake and glycolysis is insulin-independent in cardiac hypertrophy. However, evidence from loss-of-function studies is still pending to demonstrate the necessity of increased AMPK activity and to determine to what extent AMPK activation contributes to increased glycolysis in cardiac hypertrophy and failure.

Much of our understanding of the metabolic adaptations that occur during the transition of cardiac hypertrophy to failure has been garnered from studying animal models. In this regard, the translation from animal studies to the human population remains a serious
challenge. For example, down-regulation of PPARα is not evident in human heart failure and the expression level of PGC-1 in human failing hearts is variable, with the most recent reports showing a down-regulation of oestrogen-related receptor α rather than PGC-1.54,55 Although evidence that the human failing heart is energy ‘starved’ suggests a strong link to mitochondrial dysfunction,56 mechanisms contributing to altered substrate metabolism in human failure are much more complex than in animal models. The only available method in assessing myocardial glucose and fatty acid uptake and utilization is by positron emission tomography (PET). The PET study is not routinely used clinically and its results are influenced by myocardial perfusion, plasma fatty acid levels, and insulin sensitivity. A number of conflicting results have been reported in heart failure patients depending on aetiology and co-morbidity.57–61 Therefore, further experimentation elucidating the differences in animal and human models are warranted.

4. Pentose phosphate pathway in the hypertrophied heart

The PPP allows for an alternative fate of glycolytic intermediates. The pathway has been identified in the cytosol of all cells and is divided into two branches (Figure 1): oxidative PPP and non-oxidative PPP.62 The primary function of the oxidative PPP is to form NADPH, which is important in combating reactive oxygen species by maintaining reduced glutathione levels. The oxidative PPP utilizes G-6-P created from the initial reaction of glycolysis as a substrate through the action of glucose-6-phosphate dehydrogenase (G6PD). In the non-oxidative PPP, formation of ribose-5-phosphate and/or xylulose-5-phosphate is important in nucleotide or nucleic acid synthesis or as a possible transcriptional signalling molecule, respectively.63,64 Although this pathway is present in all cells, its overall importance in normal cardiac metabolism is believed to be minor.15,65,66

Early studies reported an up-regulation of the PPP in cardiac hypertrophy.67,68 Activity of the regulatory enzyme, G6PD, has been shown to be elevated in animal models of pressure overload69 and a canine model of heart failure,70 whereas no changes in the flux or enzymes involved in oxidative or non-oxidative PPP in hypertrophied hearts have been found.15,71 Of note, mice deficient in G6PD had increased ischaemia-reperfusion injury, alluding to the importance of the PPP in protection against oxidative injury.72 However, recent studies suggest that excessive NADPH derived from the oxidative PPP contributes to cardiomyopathy and heart failure.70,73 Thus, whether the observed increases in G6PD are beneficial or detrimental in the development of pathological cardiac hypertrophy and failure requires further investigation.

5. Other pathways for glucose metabolism in the hypertrophied heart

Glycogen metabolism has been shown to be an active process that contributes to glycolysis especially during periods of increased work and ischaemia.65–74 Both normal and pressure-overloaded hearts possess similar glycogen content at baseline and have equal rates of glycogen contribution to glycolysis, especially during low-flow ischaemia.27,77 However, hypertrophied hearts preferentially oxidize glucose from glycogen stores as opposed to exogenous glucose,27 suggesting an enhanced glycogen turnover rate, specifically detected during an interval of severe ischaemia.28 Despite this, there does not appear to be an appreciable difference in the contribution of glycogen metabolism to the metabolic profile in the hypertrophied heart.

Increased glucose entry affords an opportunity for the recruitment of the HBP (Figure 1). This pathway converts F-6-P to the principal end product uridine diphosphate-N-acetylgalcosamine (UDPGlCNac).78 UDPGlCNac can subsequently be used for the O-linked glycosylation of a variety of proteins through the actions of transferases.79 To this end, a recent study showed that one of these proteins, O-linked β-N-acetylgalosamine transferase, was elevated in a mouse model of heart failure.80 Additionally, increased amounts of UDPGlCNac and increased gene expression of the rate-limiting enzyme, glutamine fructose-6-phosphate amidotransferase (GFAT), were identified in a mouse model of pressure overload hypertrophy71 (Figure 2). Increased HBP flux may promote protein O-linked β-N-acetylgalosamine glycosylation (O-GlcNAcylation). It has been shown that increased O-GlcNAcylation resulted in cardiomyocyte dysfunction associated with decreased sarcoplasmic reticulum Ca2+-ATPase expression and abnormal calcium transients in cardiomyocytes exposed to hyperglycaemia or from diabetic rats.81,82 In addition, increased glycosylation has been linked to increased apoptosis.83

Recent studies have also suggested that glucose metabolism regulates protein acetylation in many cell types84,85. Multiple enzymes involved in glycolysis, β-oxidation, and the TCA cycle were acetylated in liver tissue in response to glucose or fatty acids.85 More recently, acetylation of myosin heavy chain isoforms was found in cardiac hypertrophy which resulted in increased affinity between actin and myosin with a higher sliding velocity, suggesting a possible mechanism for enhanced contractile performance of the hypertrophied myocardium.86 Overall, post-translational modifications via glycosylation and acetylation in cardiac hypertrophy is unexplored. As these modifications are dependent on cell metabolism, they potentially are important mechanisms connecting altered cardiac metabolism to the pathogenesis of heart failure, hence, an attractive future direction of research.

A surplus of G-6-P may also be converted to sorbitol via the enzyme AR in the polyol pathway (Figure 1). Increased flux through this pathway is linked to abnormal glucose metabolism in diabetes. In human studies, an approximate two-fold increase in gene expression of AR was noted87 while AR inhibition was associated with increased cardiac function in diabetic patients.88 In perfused rodent hearts and cardiomyocytes, cardiac dysfunction and abnormal calcium transients under high-glucose conditions were abolished with an AR inhibitor.89 Using mouse models to study this pathway is problematic as the levels of AR expression and activity are much lower in mice than in humans; however, overexpression of the human form of AR is associated with impaired functional recovery after ischaemia.90 The exact role that the polyol pathway plays in the development of cardiac hypertrophy is yet to be elucidated.

6. The functional consequence of altered glucose metabolism in cardiac hypertrophy

Because of its association with the ‘foetal profiles’, increased glucose utilization in cardiac hypertrophy was initially considered maladaptive.
However, results from bioengineered mouse models with enhanced or reduced glucose utilization have demonstrated that glucose reliance in the adult heart is not harmful while reduced ability to utilize glucose is detrimental in cardiac hypertrophy and failure. For example, mice overexpressing the insulin-independent glucose transporter GLUT1 in the heart have increased glucose uptake, a high glycolytic flux partially uncoupled with glucose oxidation, and a concomitant decrease in FAO.91–94 These mice lived a normal lifespan with unaltered cardiac function despite demonstrating a foetal-like metabolic profile.93 When subjected to pressure overload by aortic constriction, they were protected against the development of cardiac dysfunction and left ventricular dilatation.91 Conversely, deletion of the insulin-sensitive glucose transporter GLUT4 or the insulin receptor in the heart results in cardiac dysfunction and poor outcome in response to hypertrophic stimuli.95,96 Furthermore, pharmacological compounds that improve insulin signalling, such as glucagon-like peptide, decreased circulating fatty acid levels and increased myocardial glucose uptake, which were beneficial in the short-term treatment of heart failure in both animal experiments and clinical studies.28,97–100 It is also important to recognize that these approaches have changed not only the relative contribution, but also the capacity of glucose utilization. The resultant benefit could be attributed to the improved oxidative ATP production.

Pharmacological inhibition of CPT1, a key regulator of mitochondrial fatty acid uptake, has been shown to partially reduce FAO and, subsequently, enhance glucose oxidation. Treatment with these compounds has demonstrated positive outcomes in animal models of heart failure. The use of oxfenicine in a canine model of heart failure resulted in an attenuation of LV dilation and wall thinning while maintaining gene expression of key enzymes involved in cardiac energy metabolism.101 In rodent models of heart failure, etomoxir enhanced myocardial performance through partial normalization of myosin isozymes102 and improvement of sarcoplasmic reticulum calcium uptake.103 Recently, short-term treatment with perhexiline, in conjunction with standard therapeutic interventions, in patients with chronic heart failure was sufficient to improve cardiac function and peak exercise oxygen consumption. Another partial FAO inhibitor, trimetazidine, led to improved LV systolic and diastolic function in elderly patients with ischaemic cardiomyopathy.104

Although the preponderance of evidence is in favour of enhancing glucose metabolism in the failing myocardium, a recent clinical study provided contradictory evidence. Administration of an inhibitor of lipolysis in patients with dilated cardiomyopathy resulted in a significant decrease in myocardial fatty acid uptake, which was associated with decreased cardiac work and myocardial efficiency.105 Since FAO is responsible for the majority of energy supply in the normal heart, strategies focusing on preventing the deficiency of FAO in the failing heart seem reasonable. However, enhancing FAO by targeting PPARα has not provided convincing conclusions. Overexpression of PPARα resulted in contractile dysfunction while reactivation of PPARα with an agonist in a model of pressure overload hypertrophy resulted in impaired response to myocardial ischaemia.34,106 Chronic activation of PPARα with fenofibrate in rats post-MI or in dogs with pacing-induced heart failure maintained the FAO gene profile but had modest benefits on the development of heart failure.107,108 Recently, several studies suggested that high-fat diet protected against the development of heart failure in rat models.59,109,110 Of note, this coincides with the clinical observation of the “Obesity Paradox”, in which patients with a high body mass index (BMI) have reduced mortality from heart failure.111,112 Although the mechanisms underlying the benefits of a high-fat diet in rats and/or obesity in heart failure patients are unknown, the observations clearly challenge the concept that fatty acids are detrimental to the failing heart.

Recently, several studies have begun to manipulate relative substrate oxidation at the point where they enter the mitochondria using engineered mouse models with cardiac-specific overexpression or deletion of pyruvate dehydrogenase kinase or acetyl-CoA carboxylase 2.113–115 These models should yield valuable information specific to the changes in substrate oxidation in cardiac hypertrophy. However, it is also important to bear in mind the limitations of these models. For example, the baseline metabolic phenotype present at birth could trigger compensatory mechanisms that confound the response to a pathological stimulus. Additionally, the biased use of one particular substrate prior to the induction of pathological hypertrophy could confine the ability to detect therapeutic strategies. Therefore, it is worthwhile to investigate cases in which the metabolic perturbation occurs after cardiac hypertrophy is present.

7. Summary and future perspectives

Research using animal models in the past several decades has consistently demonstrated that the hypertrophied heart possesses an altered metabolic profile that is similar to the foetal heart. Several plausible mechanisms have been proposed that have substantially enhanced our understanding of the metabolic regulation during chronic stress. The challenge we now face is the translation from animal studies to patients to identify therapeutic opportunities. Here, it is important to recognize that human diseases differ from the animal models not only by the fundamental biology, but also by the co-morbidity and environmental inputs such as diet and medications. Most of the work in the past decade has focused on the relative oxidation of fatty acids vs. glucose in the heart. These efforts have collectively shown that there is no single good or bad substrate for the heart, and that maintaining a metabolic flexibility is critical for normal cardiac function. Therefore, the future work should be directed to improve the overall capacity for ATP generation while maintaining a balance of substrate supply and utilization. Furthermore, the changes in the non-energy producing pathways of substrate metabolism may play equally important roles in the disease mechanisms and deserve equal attention in our future research.

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