Glucose for the Aging Heart?

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Aging is associated with increased susceptibility of the heart to ischemia. Many potential reasons for this exist, including increased oxidative stress, mitochondrial dysfunction, and possibly changes in myocardial substrate utilization.\(^1\) Given the fact that ischemic heart disease is the leading cause of death in the aging population, strategies that increase the ability of the heart to recover after ischemic insults could have important therapeutic benefits. In a report published in this issue of *Circulation*, Luptak and colleagues describe the susceptibility of isolated hearts from mice with lifelong overexpression of the GLUT1 glucose transporter to ischemia and reperfusion.\(^3\) They report that a long-term increase in glucose utilization limits age-related diastolic dysfunction and is associated with a reduction in ischemic contracture during low-flow ischemia and improved recovery of systolic and diastolic function after reperfusion. Importantly, overexpression of the GLUT1 transgene was associated with reduced rates of depletion of cardiac ATP stores during ischemia that were particularly striking in young mice, higher concentrations of phosphocreatine at baseline in older mice, and a more rapid restoration of high-energy phosphate content in the hearts of young and old transgenic mice after reperfusion. Thus, maintaining high rates of myocardial glucose utilization might retard age-related myocardial dysfunction and promote functional recovery after ischemia.

To maintain high rates of ATP generation, the heart exhibits a remarkable ability to metabolize a variety of metabolic substrates. It is widely accepted that under physiological circumstances, oxidative metabolism of fatty acids accounts for >50% of myocardial ATP generation in the nonstressed heart, with the remaining energy being derived from metabolism of lactate, ketone bodies, and glucose.\(^4\) Glucose entry into the heart is mediated via members of the facilitative glucose transporter family. This family has 12 members (GLUT1–12) with varying tissue distribution and subcellular localization. The glucose transporters that are expressed at significant levels within the heart are GLUT1, GLUT4, GLUT8, GLUT11, and GLUT12.\(^5\) Of these transporters, the most highly expressed and comprehensively characterized have been GLUT1 and GLUT4. GLUT1 resides predominantly in the sarcolemma and mediates basal myocardial glucose uptake particularly in quiescent cardiac myocytes. GLUT4 resides in a specific intracellular vesicular compartment and translocates to the plasma membrane in response to cardiomyocyte contraction, insulin, and ischemia.\(^6\) GLUT1 and GLUT4 both contribute to the regulation of basal glucose uptake in the contracting heart. Thus, in hearts that are deficient for GLUT4, basal glucose uptake is mediated in part via increased expression of GLUT1.\(^8\) However, under fasting conditions, myocardial glucose uptake in GLUT4-deficient hearts is markedly reduced.\(^9\) Conversely, in the hearts of mice with cardiomyocyte-restricted deletion of insulin receptors (CIRKO), a 75% reduction occurs in GLUT1 content and a 2- to 3-fold increase in GLUT4 content. Consistent with a role in maintaining glucose uptake into quiescent cells, basal rates of glucose uptake were markedly reduced in isolated cardiomyocytes from CIRKO mice, but in beating heart preparations and in vivo, a 2-fold increase occurred in glucose uptake that paralleled the increase in GLUT4.\(^10\) Transgenic manipulation of either GLUT4 or GLUT1 expression in the heart has been shown to increase myocardial glucose utilization. Thus, germline overexpression of a GLUT4 minigene regulated by its native promoter increased myocardial GLUT4 content by 40%, increased myocardial glucose uptake by 2-fold, and increased glycolytic rates by 1.5-fold. This modest degree of GLUT4 overexpression prevented the decrease in glucose utilization and increase in myocardial fatty acid (FA) utilization that accompanies diabetes in db/db mice and prevented diabetes-induced cardiac dysfunction.\(^11\) The transgenic mice that are reported by Luptak et al in the present study have >20-fold overexpression of GLUT1 and a 40-fold increase in basal rates of glucose uptake. GLUT1 overexpression allowed these hearts to maintain their function after long-term pressure overload and rescued the defect in contractile reserve of peroxisome proliferator-activated receptor (PPAR)-\(\alpha\)-deficient hearts that exhibit reduced FA oxidative capacity.\(^13\)

In pathophysiological states, important changes occur in patterns of myocardial substrate utilization. Thus, in pressure overload cardiac hypertrophy, a switch takes place toward increased glucose utilization and a reduction in FA utilization mediated in part by transcriptional repression of peroxisome proliferator-activated receptor gamma coactivator 1 and the expression of PPAR-\(\alpha\)-regulated genes and an increase in the activity of AMP kinase.\(^15\) In contrast, in diabetes mellitus an increase occurs in myocardial FA utilization and a reduction in glucose utilization driven in part by reduced expression of glucose transporters, increased delivery of FA to the heart, and activation of PPAR-\(\alpha\)-regulated genes.\(^4\) In both of these
scenarios, progressive left ventricular dysfunction occurs. Although it is widely accepted that the increased FA utilization and decreased glucose utilization that develop in diabetic hearts are ultimately maladaptive, there has been debate on whether the increase in glucose utilization in hypertrophied hearts represents a beneficial adaptation or is ultimately maladaptive. Hearts that are deficient in proliferator-activated receptor gamma coactivator 1α exhibit a more rapid transition to heart failure than control hearts after pressure overload, and mice that lack expression of lipoprotein lipase in cardiomyocytes also are unable to maintain function after pressure overload despite greatly increased levels of glucose utilization.16,17 Similarly, in human studies, pharmacological inhibition of FA utilization was associated with a decline in cardiac function in patients with dilated cardiomyopathy.18 In contrast, increasing FA utilization in hearts with pressure overload hypertrophy by activating PPAR-α signaling pathways leads to a rapid deterioration in contractile function.19 Taken together, these observations suggest that an obligate requirement exists for FA metabolism in the hypertrophied and failing heart; however, the “therapeutic index” might be narrow, given that attempts to reengineer hearts to increase myocardial FA utilization by increasing the expression of FA transporters, acyl coenzyme A synthase, or PPAR-α ultimately lead to contractile dysfunction,20 which can be improved by limiting FA uptake.21 The same concern does not seem to be the case for glucose, however.

The studies by Tian and colleagues3,13,14 suggest that an increase in glucose availability might be beneficial in the context of cardiac hypertrophy and cardiac aging and in the response of the heart to ischemia. Studies in mice deficient in malonyl coenzyme A decarboxylase that develop a substantial increase in glucose utilization at the expense of FA utilization also exhibit increased myocardial recovery after ischemia.22 However, the beneficial effect of glucose in the present study might not be completely attributable to a switch in substrate utilization toward glucose and away from fatty acids. This is because rates of FA utilization were not decreased in young GLUT1 transgenic hearts that clearly exhibited enhanced preservation of systolic and diastolic function after ischemia and reperfusion. Moreover, an increase in glucose utilization in PPAR-α– or lipoprotein lipase–deficient hearts does not seem to be sufficient to maintain contractile reserve in the heart in the face of hemodynamic stress.14,17 Therefore, it would appear that increasing glucose uptake into the heart confers additional benefits over the long term when glucose metabolism exceeds normal cardiac requirements. What might these mechanisms be? One possibility is an increase in glycolytic ATP generation, which may contribute to the maintenance of increased myocardial high-energy phosphate content, particularly during reperfusion. Additional evidence for a role for glucose uptake in maintaining high-energy phosphate content in the heart after reperfusion was obtained previously in hearts that were deficient for the GLUT4 transporter selectively in cardiomyocytes. In these experiments, a reduction in glucose uptake in fasted GLUT4-deficient hearts correlated with a significant acceleration in ATP depletion during ischemia and reduced restoration of phosphocreatine after reperfusion.9 Similar observations have been made in mice with reduced AMP-activated protein kinase activation that also exhibit a reduction in postischemic myocardial glucose utilization.23,24 A second potential benefit of a chronic increase in myocardial glucose uptake is the expansion of the myocardial glycogen pool. Although in the present study it does not appear that increased glycogenolysis could account for the protection from ischemic injury in GLUT1 transgenic mice, the possibility exists that this increased glycogen pool could be beneficial during more severe ischemia (global versus low flow) or if ischemia is more prolonged.

An important question raised by the present study is whether the beneficial effects of GLUT1 overexpression in the aging heart can be fully attributable to changes in myocardial metabolism. One nonmetabolic mechanism by which increased GLUT1 expression could lead to cardioprotection is a reduction in apoptosis. An increase in GLUT1 expression was shown in cultured cardiomyocytes to confer resistance to apoptosis that could be dissociated from an increase in glucose transport.25 Therefore, it would be of interest to determine whether apoptosis is decreased when GLUT1 transgenic hearts are subjected to ischemia. Increased glucose uptake in the heart is associated not only with an increase in flux through glycolysis but also with increased flux via other pathways that utilize glycolytic intermediates. These pathways include increased flux of fructose-6-phosphate through the hexosamine biosynthetic pathway and increased generation via dihydroxyacetone phosphate of diacylglycerol, which activates protein kinase C and increased generation of methylglyoxal from triose phosphates, which ultimately contributes to the accumulation of advanced glycation end products. Activation of these pathways has been proposed to contribute to diabetic complications, including cardiomyopathy.26 It is intriguing therefore that GLUT1 transgenic mice do not appear to exhibit any untoward consequences of increased glucose utilization.

Activation of the hexosamine biosynthetic pathway leads to the generation of glucosamine-6-phosphate from fructose-6-phosphate. Uridine diphosphoglucose-N-acetylglucosamine is the end product of this pathway and is the substrate for O-linked glycosylation of many cellular proteins. Increased flux through this pathway and increased glycosylation of regulatory proteins such as Akt and glycogen synthase have been shown to contribute to the pathogenesis of insulin resistance and have been proposed to contribute to the pathogenesis of diabetic complications.26 On the other hand, the Chatham group27 has shown in a series of studies that increased hexosamine flux and increased protein O-glycosylation may increase the resistance of hearts to ischemic injury. Thus, it would be of interest to determine whether the hexosamine biosynthetic pathways are activated in the hearts of GLUT1 transgenic mice and to determine the extent to which this might contribute to cardioprotection in this model. It is not clear why hexosamine pathway activation is beneficial in the heart but potentially deleterious in vascular smooth muscle cells, for example. It is likely that differences might reflect differential protein targets of O-glycosylation in the heart versus other tissues, and this is a fertile area for future studies. Moreover, it will be critical to
determine whether GLUT1 transgenic mice will be sensitized to the potential deleterious effects of hyperglycemia and increased myocardial delivery of lipids, as would occur in obesity and diabetes, which occur with increased frequency in the aging population.

Whereas the study by Luptak and colleagues shows that lifelong overexpression of GLUT1 may confer a protective benefit in the aging heart, particularly in terms of ischemia tolerance, the possibility exists that this represents the consequences of long-term adaptations that ultimately result in cardioprotection. Thus, it will be of interest to determine the nature of the adaptations. For example, does a lifelong increase in glucose utilization reduce oxidative stress, or does it lead to the reprogramming of transcriptional networks that might contribute to the phenotypes observed? This is an important caveat in extrapolating the results from these studies to the management of myocardial ischemia in the elderly. In other words, will strategies that will acutely increase glucose utilization in the hearts of the elderly lead to cardiac protection in the context of ischemic injury? It is unlikely that a lifelong increase in glucose uptake will become a viable therapeutic strategy, but ways exist through which myocardial glucose utilization could be increased in the short term. For example, reducing FA utilization with trimetazidine, malonyl coenzyme A decarboxylase inhibitors, or inhibitors of lipolysis or administering insulin and glucose should increase myocardial glucose utilization in the context of ischemia. A number of clinical studies have examined the effect of insulin and glucose infusion in the context of acute myocardial ischemia. Results of these studies are mixed, with some showing benefit and others not. Insulin therapy in the context of ischemia not only increases myocardial glucose utilization but also reduces myocardial FA utilization and systemic glucose concentrations. Indeed, it would appear that reducing hyperglycemia in the context of critical illness and acute myocardial ischemia might represent the important mechanism that confers a survival benefit. Thus, the efficacy of short-term modulation of myocardial glucose utilization per se as a therapeutic strategy to reduce cardiac injury in acute coronary syndromes remains an open question. Therefore, it will be invaluable to develop mouse models with inducible increases in myocardial glucose utilization to determine whether a short-term increase in myocardial glucose uptake will still confer cardioprotection in the aging heart when those hearts are subjected to ischemic injury. Second, it will also be important to subject GLUT1 transgenic mice to coronary artery ligation with and without reperfusion in vivo to determine whether these hearts remain protected in the context of an intervention that might more closely mimic the scenario that is observed clinically in patients with acute coronary syndromes.

In summary, the present study provides strong evidence to support the potential benefit of increasing myocardial glucose utilization in the aging heart. Although enhanced generation of ATP via glycolysis might represent an important mechanism that is responsible for these benefits, it is also likely that additional mechanisms exist. It is possible that a long-term increase in myocardial glucose utilization results in metabolic and transcriptional reprogramming in the heart that contribute to the cardioprotective phenotype in these mice. Elucidation of the nature of the adaptations will be of great value because they might identify pathways or targets that might be more amenable to short-term therapeutic manipulations, thereby allowing these observations to be translated more rapidly to the clinic.

Acknowledgments

Because of space limitations, primary sources could not be cited for all of the studies discussed in this editorial.

Sources of Funding

Dr Abel is an Established Investigator of the American Heart Association. Research studies in the Abel laboratory that have contributed to this review were supported by National Institutes of Health grants UO1 HL70525, UO1 HL087947 (Animal Models of Diabetes Complications Consortium), RO1 HL70070, and RO1 HL73167.

Disclosures

None.

References


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Circulation. 2007;116:884-887
doi: 10.1161/CIRCULATIONAHA.107.723015
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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