Energy metabolism in the heart of the diabetic patient

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Abstract

Because of the combined effects of insulin resistance and high concentrations of circulating fatty acids in the uncontrolled diabetic state, cardiac myocytes use fatty acids almost exclusively to support ATP synthesis. Reliance on fatty acid oxidation for ATP production results in greater mitochondrial oxygen consumption costs compared with glucose oxidation. Fatty acids can induce uncoupling of mitochondria, probably by upregulation of uncoupling proteins (UCPs). Two uncoupling protein isoforms, UCP2 and UCP3, are present in the human heart. The activity of these proteins decreases the mitochondrial proton gradient without the generation of ATP, and thereby decreases myocardial energy production. Their expression correlates positively with fasting plasma FFA concentrations. In parallel, there is a decrease in insulin-responsive glucose transporter function and glucose oxidation. Alterations in myocardial energetics occur early in the pathophysiology of type 2 diabetes and appear to precede measurable alterations in in-vivo cardiac function.
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Keywords: Cardiac energy metabolism, diabetes, fatty acid utilization, mitochondrial uncoupling

Introduction

It is well recognized that patients with diabetes mellitus have an increased risk of cardiac disease that is independent of the presence of secondary risk factors such as coronary artery disease [1,2]. A large body of evidence now indicates that cardiac metabolism and disease are intimately related [3,4]. In the normal adult heart, free fatty acids (FFAs) and carbohydrates (glucose and lactate) are metabolized for permanent cellular energy (ATP) production in the mitochondria. However, in the diabetic heart, glucose and lactate oxidation are decreased and fatty acid oxidation is increased. The increased reliance on fatty acid oxidation arises from the interplay of depressed insulin signaling, with associated consequences in the control of myocardial glucose uptake and utilization, and increased circulating concentrations of FFAs. Few studies have assessed insulin-stimulated glucose metabolism in the myocardium of patients with diabetes. Those studies that have used positron emission tomography to determine insulin-stimulated uptake of fluorine-18-labeled fluorodeoxyglucose have clearly shown that type 2 diabetes is specifically associated with severe insulin resistance, regardless of coronary artery disease and despite normal basal blood flow [5,6]. Because of the importance of insulin in the control of myocardial glucose uptake and utilization, the flexibility for metabolic substrate use is then lost, and cardiac myocytes use fatty acids almost exclusively to support ATP synthesis.

Metabolic disturbances in cardiac myocytes

Reliance on fatty acid oxidation for ATP production results in greater mitochondrial oxygen consumption costs compared with glucose oxidation, and

calculations of the yield of ATP per oxygen atom consumed (P/O) show that fatty acids are a less efficient fuel when compared with glucose. In other words, more oxygen is required for ATP production when hearts are metabolizing fatty acids than when they utilize glucose. However, the theoretical difference in cardiac efficiency based on calculations of P/O ratios for fat and glucose metabolism appears to be greater than expected when the utilization of lipid is increased [7]. This discrepancy feeds the argument that fatty acids can induce uncoupling of mitochondria, perhaps by upregulation of the expression and activity of uncoupling proteins. Uncoupling proteins are mitochondrial transporters present in the inner membrane of mitochondria. They belong to the family of anion mitochondrial carriers that includes adenine nucleotide transporters. The term ''uncoupling protein'' (UCP) was originally used for UCP1, which is uniquely present in mitochondria of brown adipocytes [8]. UCP1 catalyzes a highly regulated proton leak, converting energy stored within the mitochondrial proton electrochemical potential gradient to heat. This uncouples fuel oxidation from conversion of ADP to ATP, resulting in decreased synthesis of ATP [9]. Two uncoupling protein isoforms, UCP2 and UCP3, are located in the heart [10]. The expression of mitochondrial UCP2 and UCP3 that are present in human hearts correlates positively with fasting concentrations of plasma FFAs [10]. In parallel, there is a decrease in insulin-responsive glucose transporter 4 protein. It is also worth noting that fatty acids reduce the action of insulin by inhibiting insulin signaling pathways [11], leading to a decrease in glucose transporter function and further reduction in glucose oxidation.

Mitochondrial energy production

As mentioned above, the activity of UCP2 and UCP3 proteins decreases the mitochondrial proton gradient without the generation of ATP, and thereby decreases myocardial energy production. This process could explain why human phosphocreatine (PCr) to ATP ratios correlate negatively with plasma FFA concentrations [10]. It should be noted in this context that patients with heart failure have also increased plasma FFA concentrations, high whole-body insulin resistance, and low insulin-stimulated uptake of fluorodeoxyglucose in the heart [10,12,13]. A recent study of mitochondrial energetics in hearts of leptin receptor-mutant (*db/db*) type 2 diabetic obese mice has demonstrated that mitochondrial uncoupling is indeed mediated by activation of uncoupling proteins [14]. This probably occurs on the basis of increased delivery of the reducing equivalents $FADH_2$ and NADH from fatty acid oxidation, coupled with a reduced ability for complete oxidation of these equivalents. This might contribute to increased generation of mitochondrial reactive oxygen species (ROS) which, in turn, activates uncoupling proteins. Mitochondrial uncoupling may *initially* represent an adaptive response to increased fatty acid oxidation and fatty-acid-mediated generation of reactive oxygen species. However, it does not completely normalize the overproduction of mitochondrial reactive oxygen species, as demonstrated by the accumulation of products of lipid peroxidation [14]. Therefore the negative impact of mitochondrial uncoupling is to reduce the mitochondrial supply of ATP. Altered myocardial energetics characterizes these hearts and clearly precedes measurable alterations in in-vivo cardiac function, as assessed by echocardiography [14,15]. Cardiac high-energy phosphate metabolites, measured at rest in patients with type 2 diabetes using phosphorus-31 nuclear magnetic resonance spectroscopy, have revealed a decrease in PCr to ATP ratios [15]. Furthermore, data have underlined that not only do alterations in cardiac energetics occur early in the pathophysiology of type 2 diabetes, but these alterations are correlated negatively with the fasting plasma FFA concentrations. Defective energy metabolism in the heart is likely to impair energy-requiring processes and therefore myocardial function, cardiac contractile performance, and diastolic function [4], the last of these being a hallmark phenotype of diabetic cardiomyopathy in the earlier stages. This may also limit the ability of the myocardium in patients with type 2 diabetes to withstand ischemia, and may contribute to the increased cardiovascular morbidity and mortality in such patients [16].

Conclusion

The evidence available at present highlights the complexity of alterations in myocardial cell metabolism that may be associated with a multifactorial disease such as diabetes, especially type 2 diabetes. Target tissues become resistant to the effects of insulin, and fatty acids probably have a critical role in the development of cellular insulin resistance [11]. Certainly, there are similarities in cardiac dysfunction in animal models and human type 2 diabetes or obesity, or both. For instance, obese young women showed increased cardiac utilization of fatty acid as measured by positron emission tomography, and increased myocardial oxygen consumption, with reduced cardiac efficiency [17]. Numerous detrimental effects ensue from the loss in myocardial substrate flexibility, and can lead to impaired left ventricular function.

Further supporting the metabolic–functional relation are studies in experimental models of diabetes demonstrating that reversing metabolic alterations results in improved contractile function. The metabolic improvements are paralleled by a more

favorable energetic profile and improved left ventricular function. The success of experimental studies has led to the investigation of myocardial metabolic manipulation in patients with type 2 diabetes. Recent work has investigated high-energy phosphate metabolism in a well controlled diabetic population in which only men with short duration (~3–4 years) type 2 diabetes were included [18]. In this population, in which the extent of left ventricular dysfunction was limited to subtle abnormalities in diastolic function, the PCr to ATP ratio was similar to that observed in normal controls, and no correlation was found between increased myocardial glucose uptake induced by pioglitazone and high-energy phosphate metabolism. Conversely, another study that used phosphorus nuclear magnetic resonance spectroscopy in patients with type 2 diabetes (both men and women) clearly showed significantly altered cardiac high-energy phosphate metabolism, despite still apparently normal cardiac morphology and function [15].

These data, in accordance with those obtained in hearts of diabetic *db/db* mice [14], indicate that alterations in cardiac energetics occur early in the pathophysiology of type 2 diabetes and are associated with alterations in circulating metabolic substrates. These findings suggest that chronic manipulation of the myocardial metabolic substrate, aimed at reducing fatty acid oxidation, such as can be achieved with trimetazidine [19], or at improving the coupling between fatty acid delivery and oxidation in cardiac myocytes, may prevent or slow the progression of left ventricular dysfunction in hearts of diabetic patients. ■

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