COMMENTARY

Metabolic Flexibility of Mitochondria Plays a Key Role in Balancing Glucose and Fatty Acid Metabolism in the Diabetic Heart

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In order to meet its energy requirements, the heart has the intrinsic capability to metabolize a wide range of energy substrates. In normal conditions, the heart favors fatty acids as the main energetic substrate, followed by carbohydrates, ketone bodies, and, lastly, amino acids (1,2). Yet, the myocardium is able to dynamically switch its metabolism according to substrate availability, in order to attempt to guarantee an efficient pumping function in virtually any scenario (2,3). Mechanistically, this phenomenon seems to be possible, as the different substrates available in the heart compete as source of energy, making the final choice essentially based on the relative substrate concentrations. In a seminal *Nature* article published in 1961, Schipp et al. (4) demonstrated for the first time that increasing fatty acid availability resulted in a marked inhibition of glucose oxidation. Overall, the high flexibility in selecting the most suitable fuel is considered a fingerprint of a healthy myocardium (1). Accordingly, an impaired metabolic flexibility is strongly linked to cardiac damage and dysfunction (2). In the presence of diverse pathological conditions, cardiac metabolism might lose the ability to use some substrates. Whether this phenomenon is deleterious or actually denotes an adaptive response of the myocardium to keep its metabolic rate remains controversial. However, clarifying this aspect is of crucial importance, especially in order to design new therapeutic strategies.

In this context, diabetic cardiomyopathy is one of the most critical knots to untie. In diabetes, despite the hyperglycemic status, a reduced capability to use glucose by myocardium has been reported (5,6). However, whether such impairment in glucose oxidization is an adaptive or maladaptive response of the diabetic heart remains to be elucidated. The matter is highly debated, despite recent evidence suggesting that restoring glucose utilization could have beneficial therapeutic effects: specifically, a global overexpression of GLUT4, the major mediator of myocardial glucose uptake, has been shown to improve insulin sensitivity in high-fat diet–fed mice (7) and to prevent the major abnormalities of diabetic cardiomyopathy in *db/db* mice (8). Nevertheless, this phenomenon could be attributable to the systemic amelioration of metabolic homeostasis and not only to the increased glucose utilization by cardiomyocytes, as suggested by the amelioration of insulin resistance obtained by overexpressing GLUT4 in the skeletal muscle (9). Moreover, the loss of GLUT4 seems to induce myocardial dysfunction, and the overexpression of GLUT1 can protect against contractile impairment after chronic pressure overload (1,10). Albeit these data suggest that inducing glucose uptake in cardiomyocytes could be beneficial, direct evidence showing the effects of restoring glucose uptake in diabetic myocardium is missing.

In this issue of *Diabetes*, Wende et al. (11) describe a transgenic mouse model with a conditional and specific cardiac overexpression of GLUT4, in which diabetes is obtained via streptozotocin injection. This elegant model allows to specifically address the role of glucose uptake restoration exclusively in the heart (specific cardiomyocyte knock-in) and when the glucose utilization is actually impaired (conditional knock-in after diabetes induction). The authors provide compelling data on the development of diabetic cardiomyopathy both in vivo and ex vivo. Since mitochondrial alterations have a pivotal pathogenic role in diabetic cardiomyopathy development and progression (12–14), the studies are mainly focused on mitochondrial metabolism and function. Harnessing this model, the

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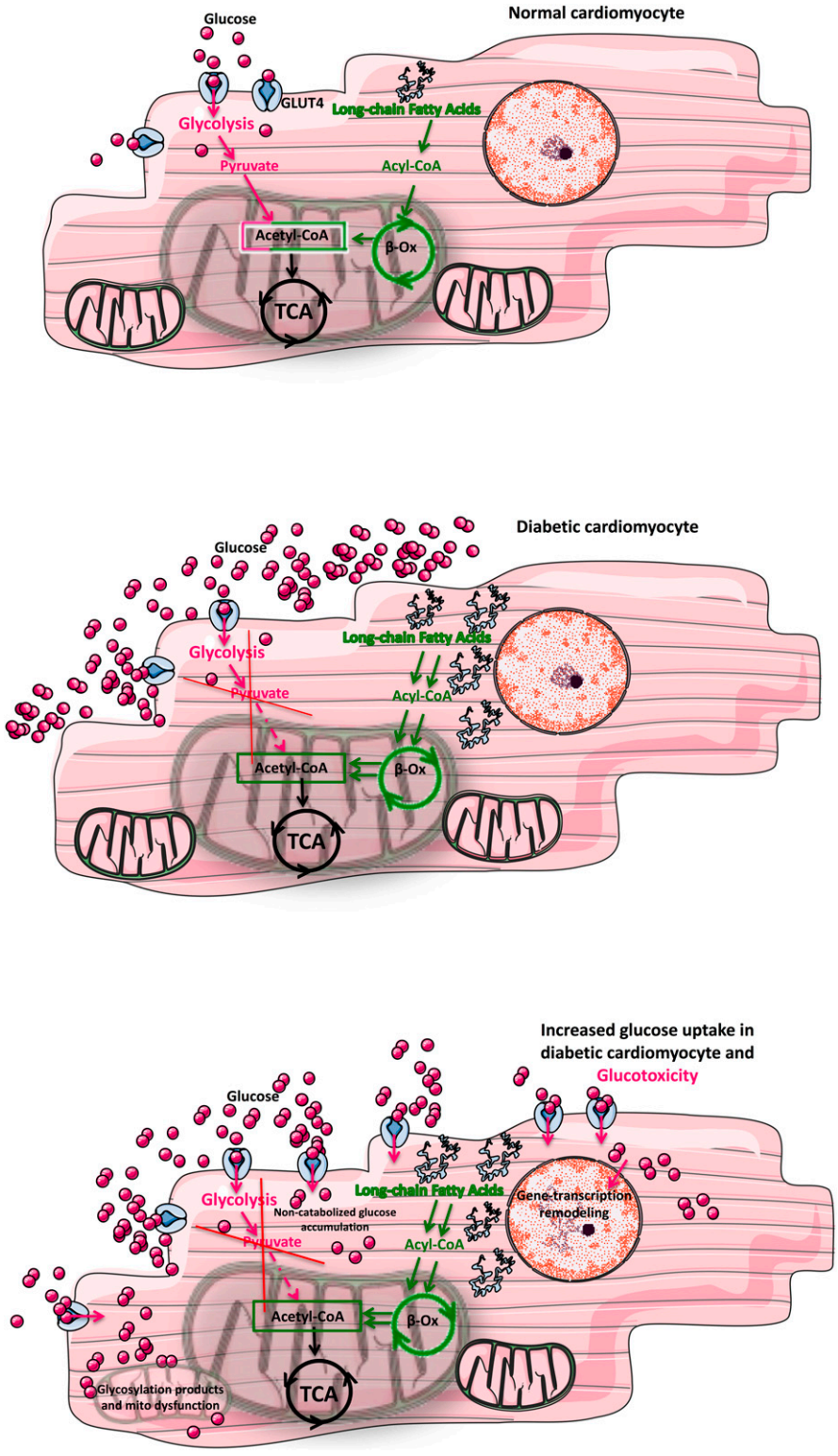

Figure 1—Metabolic competition between glucose and fatty acids in a normal cardiomyocyte, a diabetic cardiomyocyte, and a diabetic cardiomyocyte with enhanced glucose uptake. *Top*: In normal conditions, cardiomyocytes are able to use both fatty acids (green) and glucose (pink) as energy substrates, with a preference for fatty acids: acetyl-CoA molecules entering the mitochondrial tricarboxylic acid cycle (TCA, also known as Krebs cycle) derive from glycolysis and from fatty acid β-oxidation (β-Ox); in the β-Ox processes, long-chain acyl-CoA molecules—the main components of long fatty acids—are broken to acetyl-CoA molecules. *Middle*: In diabetic conditions, the excessive availability of fatty acids, mainly due to an impaired insulin signaling, engulfs the catabolic machinery, making cardiomyocytes unable to oxidize glucose. *Bottom*: The augmented glucose uptake induces intracellular accumulation of noncatabolized glucose, inducing glucotoxicity; furthermore, increased glucose levels can affect mitochondrial function by direct posttranslational modifications of the protein pool and/or by inducing a maladaptive gene transcription program.

impairment of glucose uptake and utilization by cardiomyocytes in response to streptozotocin-induced hyperglycemia is successfully reproduced. Remarkably, the restoration of cardiac glucose uptake does not ameliorate diastolic dysfunction, commonly observed in diabetic mice (15). Additionally, mitochondrial dysfunction detected in diabetic cardiomyopathy seems exacerbated by glucose uptake restoration; in particular, the activity of respiratory chain complexes is significantly impaired in diabetic cardiomyocytes overexpressing GLUT4 when compared with diabetic cardiomyocytes from nontransgenic mice.

How can we interpret these results? First and foremost, diabetic cardiomyopathy is very different, not only in terms of metabolic profile, from heart failure with reduced ejection fraction (HFrEF). Indeed, in HFrEF we generally observe metabolic remodeling mainly represented by a reduced capacity to utilize fatty acids as energetic substrate (16,17). Altered gene expression and epigenetic phenomena are involved in the impairment of the fatty acid catabolism machinery in cardiomyocytes. In this scenario, glucose represents the alternative fuel for myocardium, and it is relatively easy to appreciate that in these circumstances an augmented glucose availability can be useful, whereas glucose deprivation can be deleterious.

On the other hand, metabolic remodeling in diabetic cardiomyopathy is utterly different (18). In this diabetic context, the impaired insulin signaling induces lipolysis, which increases the availability of fatty acids; the catabolic machinery shifts toward an almost exclusive utilization of fatty acids, thereby hindering the use of alternative fuels (19,20). The resultant metabolic remodeling is characterized by an overall impaired ability of the myocardium to use glucose, leading to a diminished glucose uptake and glucose oxidative capability, eventually causing energetic inefficiency (18). In this case, the restoration of glucose uptake could not have a protective impact, as it would increase glucose levels within the cardiomyocytes, which are unable to catabolize it.

In addition, the intracellular accumulation of noncatabolized glucose can lead to glucotoxicity. The study of Wende et al. (11) provides a solid proof of this concept, unveiling the underinvestigated role of glucotoxicity in diabetic cardiomyocytes (Fig. 1). Applying technically sound approaches, the authors illustrate the molecular consequences of glucotoxicity on posttranslational modifications and on the regulation of gene expression by *N*-glycosylation of key transcription factors like SP1. In particular, they suggest a putative pathway by which SP1 glycosylation is responsible for the downregulation of the complex 1 protein NADH dehydrogenase [ubiquinone] 1 α subcomplex subunit 9 (NDUFA9), in turn responsible for the exacerbated mitochondrial dysfunction (11). In addition to NDUFA9 downregulation, which appears to be a rather slight effect, the impact of glucotoxicity on posttranslational modifications or expression of other molecular partners could synergistically contribute to the maladaptive response. In this sense, the study reveals that glucotoxicity can affect fundamental regulators of the metabolism of ketone bodies and amino acids, opening new research perspectives. For instance, our research group is currently working on identifying the molecular mechanisms underlying the potential therapeutic contribution of ketone bodies in diabetic cardiomyopathy, and we are strongly encouraged by the evidence offered by Wende et al. (11).

Nonetheless, while their study definitely represents a decisive step forward in the understanding of the adaptive metabolic responses of the diabetic myocardium, several points have to be elucidated. The long-term effects of glucose uptake restoration remain to be addressed, as the authors focused exclusively on the first stages of the disease. Equally important, the effects of glucose restoration were merely evaluated in the streptozotocin model of diabetes, and these results could not be confirmed in models of type 2 diabetes with hyperinsulinemia and insulin resistance. It is also important to consider that in the study setting presented by the authors, GLUT4 is not downregulated in response to diabetes; thus, GLUT4 overexpression could lead to excessive level of the protein rather than reproduce a restoration of its physiological levels. Lastly, the increased glucose uptake induced by GLUT4 overexpression represents only one level of intervention on cardiac glucose homeostasis, and other strategies, which could improve its oxidation rather than its transportation, remain to be explored.

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