PDC deletion: the way to a man’s heart disease

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The heart has continuous high-energy demands required to sustain efficient contraction. This is met by the metabolism of major circulating substrates (e.g., glucose, lactate, or lipids), according to availability, since the heart has a limited capacity for nutrient storage (reviewed in Ref. 16). Although fatty acid (FA) oxidation rates are invariably higher than glucose oxidation rates, glucose oxidation is more energy efficient than FA oxidation (with ~15% more ATP/O2 molecule). Glucose and lipids compete as oxidative substrates for the heart, resulting in either a glucose-FA cycle in which lipid predominates as oxidative substrate or a reverse glucose-FA cycle in which lipid oxidation may be suppressed and glucose utilization favored. In addition, cardiac fuel selection is modified in disease states. Cardiac hypertrophy and heart failure, often characterized by reexpression of fetal genes, can be associated with a preference for glycolytic glucose utilization, whereas the diabetic heart exhibits a major preference for FA as oxidative fuel (reviewed in Ref. 17).

Glucose oxidation is suppressed by phosphorylation (inactivation) of the pyruvate dehydrogenase complex (PDC) by the pyruvate dehydrogenase kinases (PDKs). The heart contains three PDK isoforms (PDK1, PDK2, and PDK4). PDK activity in cardiac myocytes is increased in a stable manner in response to increased lipid supply, uptake, and utilization and in response to insulin deficiency (reviewed in Ref. 18). PDK upregulation is likely to contribute to cardiac “metabolic inflexibility” in diabetes (reviewed in Ref. 12), where use of glucose as a metabolic fuel is greatly diminished due to a constraint on the ability to switch to glucose oxidation (2, 17). A diet high in saturated fat increases cardiac PDK4 expression (8). However, enhanced PDK4 expression in the heart is not necessarily maladaptive. Wistar rats fed on a “Western” diet, only moderately high in fat (45% of calories from fat), develop cardiac dysfunction after 8–12 mo, and it was proposed that this might reflect suboptimal induction of FA-responsive genes, as well as pdk4, due to inadequate activation of peroxisome proliferator-activated receptor-α (PPARα) compared with rats provided with a diet containing 60% of calories from fat (19). The existence of a circadian rhythm within the cardiomyocyte (23) affects the responsiveness of the heart to acute circadian changes in exogenous FA (5) and also influences expression (reviewed in Ref. 22). Pressure overload-induced cardiac hypertrophy, associated with a reliance on glucose, abolishes this diurnal variation of metabolic gene expression, thereby impairing the ability of the heart to anticipate and respond to physiological alterations within its environment (23), again a situation of metabolic inflexibility.

New research has highlighted potential mechanisms underlying altered regulation of PDKs, for example, hypoxia-induced upregulation of PDK1 expression by hypoxia-inducible factor-1 (1), acute control of PDK2 by phosphorylation by the diacylglycerol-activated and redox-sensitive protein kinase C isoform PKCθ (3), and PPARα- and FoxO1-mediated control of PDK4 gene expression (reviewed in Ref. 18). Whereas the lipooxidative transcription factor PPARα is activated by lipids, FoxO1 is repressed by insulin. As a consequence, cardiac PDK4 mRNA and protein expression in the heart are enhanced in starvation and diabetes (8, 20), situations that are associated with increased systemic FA delivery and insulin deficiency or resistance.

PDK4 null mice have lower-than-normal blood glucose levels during starvation because a higher PDC activity lowers the availability of gluconeogenic substrates (9). A further study from this group (10) described the effect of a global deficiency of PDK4 on glucose homeostasis in mice maintained on a high-fat diet to induce obesity. Whereas the wild-type mice showed increased PDK4 protein expression in skeletal muscle and diaphragm (although not in liver or kidney in this model), global PDK4 deficiency in this model of obesity lowered blood glucose, suggesting that increased expression of PDK4 (with the resultant suppression of glucose oxidation) in muscle in response to high-fat feeding contributes to the development of hyperglycemia in diet-induced obesity. An interesting observation was that exogenous FA inhibited glucose oxidation by diaphragms from wild-type but not PDK4+/− mice, indicating that PDK4 is the predominant “lipid-responsive” PDK isoform. This implies that a rise in FA supply is a necessary component in the upregulation of muscle PDK4 expression and suppression of glucose oxidation.

Sidhu et al. (15) examined the effect of complete suppression of pyruvate oxidation in heart and skeletal muscle, achieved by muscle-selective knockout of the α-subunit of the pyruvate dehydrogenase component of PDC under control of the heart/skeletal muscle-specific creatine kinase promoter. Knockout mice (H/SM-PDCKO) of both genders grew normally until weaning, but the transition from maternal milk (which is high-fat) to the normal high-carbohydrate diet at weaning had profound effects on mortality of the homozygous males, which did not survive beyond ~7 days. Female H/SM-PDCKO mice fared better, experiencing no mortality even if weaned on a normal high-carbohydrate diet. Remarkably, male H/SM-PDCKO mice survived when weaned on a high-fat diet but developed marked myocyte hypertrophy and left ventricular dysfunction. These outcomes reiterate those seen in mice with cardiac-specific overexpression of PPARα [myosin heavy chain (MHC-PPARα) mice], which, in the absence of alterations in lipid-fuel delivery, exhibit increased rates of myocardial lipid uptake and oxidation and decreased rates of glucose uptake and oxidation, the latter being associated with enhanced PDK4 mRNA expression (6, 7). Like the H/SM-PDCKO mice,
MHC-PPARα mice develop a cardiomyopathy with enhanced sensitivity to ischemia (11, 14), ventricular dysfunction (21), and cardiac hypertrophy (21). Both of these studies highlight the vital importance of glucose oxidation (and active PDC) for optimal cardiac performance and, as suggested by Sidhu et al. (15) for the H/SM-PDCKO mice, upregulation of PDK4 or absence of active PDC results in absent or limited metabolic flexibility in substrate switching.

Use of transgenic mice that express PDK4 under control of the MHC promoter showed that selective overexpression of PDK4 in the heart markedly suppresses glucose oxidation and increases FA oxidation by isolated perfused hearts (24). These findings support the concept that suppressing glucose oxidation “forces” fat oxidation. Despite the substantial change in substrate selection, hearts from young (8 wk old) PDK4 transgenic mice showed no overt cardiomyopathy or cardiac hypertrophy, suggesting that the restraint on glucose oxidation imposed by PDK4 could be overridden. Of interest, MHC-PDK4 mice show some residual PDC activity (~10% that of wild type), suggesting that protection against the development of cardiomyopathy could be conferred by a relatively low level of PDC flux. Consistent with this concept, in the study by Sidhu et al. (15), heterozygous H/SM-PDCKO female mice, which express about one-half the normal level of PDC activity consistent with random inactivation of one of the two X chromosomes in females, survive on standard high-carbohydrate/low-fat rodent diet. Enhanced anaerobic glucose metabolism is observed in ischemia, cardiac hypertrophy, and mechanical unloading (reviewed in Ref. 4). An ability to increase glucose oxidation by inhibition of FA oxidation is important for the ischemic heart because it reduces production of lactate and protons that are generated under anaerobic conditions because of a mismatch between glycolysis and glucose oxidation. Thus glucose oxidation not only improves energy efficiency but also reduces cellular acidification and damage.

The findings that transgenic mice overexpressing PDK4 show no signs of cardiac hypertrophy or abnormal cardiac function, contrasting with both H/SM-PDCKO and MHC-PPARα mice, also deserves comment. When MHC-PDK4 transgenic mice are crossed with transgenic mice expressing a constitutively active form of the calcineurin catalytic subunit (CnA) to induce cardiac hypertrophy, mice bearing both the CnA and PDK4 transgenes showed substantial fibrosis and necrosis, a reduced heart rate, and increased mortality (24). The authors hypothesized that disturbances in contractile function can be compensated for by altered metabolism and vice versa, but simultaneous disruption of energy producing and energy consuming pathways causes cardiac maladaptation and heart failure. The study of Sidhu et al. (15) lends support to this concept, particularly as it would be predicted that the cardiac hypertrophy seen in male H/SM-PDCKO mice would be concomitant with increased glycolysis but with an inability of suppressed FA oxidation to augment glucose oxidation.

In summary, Sidhu et al. (15) demonstrate an effect of PDC knockout in males (rapid death on weaning unless provided with a high-fat diet). While this might suggest that high-fat junk food from an early age is good for you if you are male and PDC deficient, hope for the Homer Simpsons among us, potential survival is jeopardized by left ventricular hypertrophy and dysfunction. Female H/SM-PDCKO mice, which show 50% of normal PDC activity, can survive on a normal diet, highlighting the survival advantage conferred by the retention of an ability to oxidize glucose. Further questions that might be addressed included whether cardiac hypertrophy in this model is entirely maladaptive or, perhaps, adaptive, for example, to increase the supply of glyceraldehyde 3-phosphate for esterification of a proportion of incoming FA, or to maintain glycogen stores and mammalian target of rapamycin pathways (see Ref. 13).

REFERENCES


