Metabolic responsiveness to insulin in the diabetic heart

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In recent decades there has been a gradual reduction in the morbidity attributable to ischemic heart disease as a consequence of smoking cessation, better recognition and treatment of hypertension, and the introduction of effective cholesterol-lowering drugs. Unfortunately, the rising global prevalence of Type 2 diabetes mellitus threatens to reverse these gains. Diabetes both accelerates the development of ischemic heart disease and adversely affects the prognosis of patients with established disease (9). A particular concern is that, in the setting of myocardial ischemia, diabetes increases the risk of developing cardiac contractile dysfunction and congestive heart failure (6, 11). Because effective cardiac contraction requires minute-to-minute production and consumption of large amounts of energy, this observation suggests that diabetes may perturb myocardial energy metabolism in ways that affect ischemic tolerance and/or mechanical efficiency.

One potential explanation for the observed association of Type 2 diabetes and cardiac failure is the characteristic increased reliance of the diabetic heart on fatty acids (relative to glucose and lactate) as an oxidative substrate. This increases the oxygen cost of cardiac ATP formation, thereby rendering the diabetic heart more susceptible to energy depletion under conditions where oxygen delivery becomes impaired and/or workload increases. This oxidative substrate switch has been attributed to the synergistic action of at least three factors: 1) substrate competition in the setting of increased fatty acid availability in diabetic blood (12); 2) fatty acid-induced changes in transcription of genes involved in cardiac substrate selection and mitochondrial metabolism, mediated through activation of the nuclear receptor peroxisome proliferator-activated receptor-α (2); and 3) the impaired metabolic insulin responsiveness of the diabetic heart, which should reduce its capacity for insulin-stimulated cardiac glucose uptake. Loss of metabolic insulin responsiveness would presumably be a maladaptive change for the diabetic heart because it would increase the oxygen cost of ATP formation. Furthermore, by impairing the heart’s ability to quickly switch from fat to glucose oxidation, insulin resistance would reduce cardiac “metabolic flexibility” in the face of changing workload and/or oxygen availability (16).

Recently, useful insights into the clinical relationship between Type 2 diabetes and cardiac dysfunction have begun to emerge from studies applying classical perfused-heart techniques to new mouse models of genetic insulin resistance. The report by Hafstad and coworkers (7) in this issue of the American Journal of Physiology-Heart and Circulatory Physiology adds importantly to this body of information. Using an antegrade-perfused working heart preparation to study the db/db insulin-resistant diabetic mouse, Hafstad et al. confirmed previous observations that under both physiological and pathological conditions of substrate availability, the db/db heart exhibits increased oxidative reliance on fatty acids and decreased reliance on glucose, relative to otherwise identical nondiabetic db/+ control mice. This diabetic substrate utilization pattern was associated with impaired cardiac mechanical function, as evidenced by reduced systolic developed pressure and cardiac output despite elevated left ventricular diastolic pressure. The oxidative preference of the db/db heart for fatty acids over glucose was independent of the perfusate concentrations of each substrate, suggesting that in this model, diabetes confers some primary impairment in the metabolic capacity for glucose oxidation independent of constraints imposed by simple substrate competition. These observations are consistent with the limited number of previous studies of db/db (1) and ob/ob (10) mouse models of Type 2 diabetes. The unique finding of Hafstad et al. (7) is that insulin substantially increased glucose oxidation and reduced fatty acid oxidation in the working db/db heart, indeed by a similar increment as was observed in the nondiabetic db/+ mouse heart. Interestingly, insulin stimulation of deoxyglucose uptake into quiescent cardiomyocytes prepared from hearts of db/db mice was severely blunted relative to nondiabetic cardiomyocytes, in contrast to observations in the perfused working heart but in agreement with previous studies in db/db cardiomyocytes (3).

The finding of Hafstad et al. (7) that working hearts of db/db mice retain at least moderate metabolic responsiveness to insulin may surprise some readers in light of previous observations in diabetic mice. The db/db mouse is a rather extreme model of Type 2 diabetes that develops severe hyperglycemia (fasting blood glucose in db/db mice in this study averaged ~40 mM) and marked resistance to insulin’s stimulation of glucose uptake by tissues of the whole body. Studies in the insulin-resistant but euglycemic ob/ob mouse that used techniques similar to those employed by Hafstad et al. have suggested that the milder form of Type 2 diabetes conferred by the ob/ob genotype is nevertheless associated with substantial impairment of cardiac insulin responsiveness (10). Indeed, it once seemed reasonable to assume the hearts of organisms with most types of insulin-resistant diabetes would be poorly responsive to the metabolic actions of insulin because the heart is a muscle exposed to the same metabolic milieu as typically insulin-resistant diabetic skeletal muscle. So, what should we make of the study of Hafstad et al. (7)? First, it should be acknowledged that the insulin concentration used (1 mM) is well above the physiological range; thus what these investigators have actually demonstrated is that maximal insulin responsiveness is preserved in the db/db heart, and we do not yet know anything about the physiologically important concept of insulin sensitivity. Second, metabolic studies in the isolated working mouse heart remain a technical tour de force prone to potential interpretive ambiguity and experimental artifacts. Some artifacts potentially associated with the in vitro perfused heart preparation (e.g., substantial glycogen depletion occurring during heart preparation and preliminary nonworking perfusion) might bias observations in the direction of making
the heart appear more responsive to insulin’s metabolic action in vitro than it would actually be in vivo. Others might have the opposite effect. Indeed, the reduction in cardiac work characteristic of the db/db phenotype would itself be expected to reduce insulin responsiveness (14, 19).

On the face of it, the interpretation of Hafstad et al. (7) that glucose metabolism in the db/db heart remains metabolically responsive to insulin, at least when insulin is administered in large doses, seems experimentally robust.

Perhaps the most intriguing aspect of this observation is that it agrees with the findings of the few studies that have addressed this same question in humans. Thus both Jagasia et al. (8), who measured insulin-stimulated myocardial glucose uptake directly with arterial-venous balance techniques, and Utria

in/en et al. (18), who estimated it indirectly using 18F-labeled deoxyglucose position emission tomography, found that impaired metabolic insulin responsiveness characterizes skeletal muscle but not heart in subjects with Type 2 diabetes. Indeed, the observation of Hafstad et al. (7) that insulin’s stimulation of glucose metabolism in the db/db heart was blunted in the presence of excess fatty acids suggests that Jagasia et al. and Utria

inen et al. (who studied subjects with Type 2 diabetes with elevated circulating levels of glucose and fatty acids) may in fact have underestimated the intrinsic metabolic insulin responsiveness of the diabetic human heart. Exactly why cardiac and skeletal muscle tissues of diabetic organisms respond differently to insulin’s metabolic action remains uncertain.

However, the observation of Hafstad and coworkers (7) that quiescent db/db cardiomyocytes were poorly responsive to insulin whereas perfused-working db/db hearts were more normally responsive, considered together with complementary data in rat heart (14, 19), suggests that repetitive contractile work is needed to maintain muscle in a state of normal metabolic insulin responsiveness.

Clinical implications. Insulin accelerates cardiac glucose consumption by a coordinated series of events, beginning with its binding to the cell membrane insulin receptor and culminating in activation of the rate-limiting enzymes of glycolysis, pyruvate oxidation, and glycogen synthesis (15). In addition to its role in normal energy homeostasis, this cardiac insulin-response system is also involved in the response to myocardial ischemia. Translocation of the insulin-sensitive glucose transporter GLUT4 to the cardiomyocyte cell membrane in response to ischemia has been observed in several species (13, 20), and experiments in cardiac-specific knockouts suggest this phenomenon is required for normal cardiac ischemic tolerance (17).

The observation of Hafstad et al. (7) that the db/db variant of Type 2 diabetes does not appear to reduce the heart’s intrinsic metabolic responsiveness to insulin suggests the expression and function of the cardiac insulin-response system may be preserved in organisms with Type 2 diabetes. If true, it may be a potential experimental target for gene therapy or pharmacological therapy aimed at improving myocardial ischemic tolerance (4).

Finally, the encouraging correspondence between the observations of Hafstad et al. (7) and previous findings in patients with Type 2 diabetes (8, 18) suggests the db/db mouse may be a particularly good model of Type 2 diabetes to use in studies characterizing the effects of this disease on the heart. Potentially interesting questions include how workload and substrate availability influence the expression of the insulin-response system in db/db hearts and how this influence is mediated; how the insulin-response system responds to ischemia in the db/db heart, and whether activating this system confers ischemic protection (5); and how insulin compares with other agents in its ability to stimulate glucose uptake and oxidation in the db/db heart.

Future studies of the db/db heart using proteomic and gene expression profiling techniques might be expected to yield particularly useful insights regarding the interaction between Type 2 diabetes and cardiac metabolism, structure, and function.

REFERENCES

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