Hexosamine biosynthetic pathway flux and cardiomyopathy in type 2 diabetes mellitus. Focus on “Impact of type 2 diabetes and aging on cardiomyocyte function and O-linked N-acetylglucosamine levels in the heart”

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The developed world is currently experiencing an epidemic of type 2 diabetes mellitus, with an estimated worldwide prevalence of >140 million cases (16). Among the end organs affected by diabetes is the myocardium, which has been demonstrated to exhibit a constellation of structural and functional abnormalities known collectively as diabetic cardiomyopathy. While historically it has been somewhat challenging to dissociate the effects of diabetes per se on the myocardium from those mediated by co-morbid conditions, studies applying Doppler echocardiographic techniques to both patients (9, 13) and rodent models of diabetes (1) have demonstrated generally consistent abnormalities of cardiac ventricular diastolic compliance attributable to cardiomyocyte hypertrophy, myocyte dropout, increased production of extracellular matrix, and impaired energy-dependent diastolic sequestration of intracellular calcium (7, 10). The effects of diabetes on the myocardium are perhaps less familiar to cardiovascular scientists and clinicians than its well-known effects on the coronary vasculature, yet diabetic cardiomyopathy nevertheless appears to have important clinical implications; for example, patients with diabetes have a substantially increased lifetime risk of congestive heart failure and are more than twice as likely to develop congestive heart failure in the setting of acute myocardial infarction as nondiabetic peers (16). These observations raise questions: does a predominant mechanism mediate the development of diabetic cardiomyopathy, and, if so, can its operation be suppressed pharmacologically?

In this issue of *AJP-Cell Physiology*, Fülop et al. (8; see p. 1370) report the latest in a productive series of examinations by their group and others of the hypothesis that increased flux of glucose carbon through the cardiomyocyte hexosamine biosynthetic pathway (HBP) is responsible for many of the manifestations of diabetic cardiomyopathy. Hexosamine biosynthesis normally represents only a minor alternative metabolic fate for glucose carbon at the fructose-6-phosphate step of glycolysis. However, HBP flux may increase under conditions of excess availability of exogenous glucose (when glucose is imported into cardiomyocytes in excess of their capacity to readily metabolize it via glycolysis and pyruvate oxidation) or free fatty acids (whose uptake and metabolism may inhibit pyruvate oxidation) (11, 12). Oxidative stress, another consistent feature of diabetes, may also increase HBP flux by inhibiting the operation of glyceraldehyde-3-phosphate dehydrogenase, the rate-limiting enzyme of glycolysis (2, 3, 6). The major product of the HBP, UDP-N-acetylglucosamine (UDP-GlcNAc), is the obligatory substrate for O-GlcNAc transferase (OGT), an enzyme that catalyzes the reversible O-GlcNAcylation of specific serine/threonine residues of numerous cytosolic and nuclear proteins (4). Posttranslational O-GlcNAcylation likely interferes with serine/threonine phosphorylation of these same proteins, thereby altering their function. Because protein substrates for OGT include broad-specificity nuclear transcription factors and insulin-responsive metabolic enzymes resident in the cytosol, the HBP has been hypothesized to function as a cellular “fuel gauge” in which increased HBP flux mediates the development of insulin resistance as a brake on excessive glucose consumption (4, 12).

The significance of the HBP for diabetic cardiomyopathy resides in a broad series of recent observations in isolated cardiomyocytes and insulin-deficient rat models that demonstrate that cardiomyocyte excitation-contraction (E-C) coupling and ionotrophic reserve are sensitive to cellular levels of UDP-GlcNAc and, correspondingly, to the balance between the activities of OGT and its counterpart, O-GlcNAcase (5, 10, 14). These observations support the general premise that increased protein O-GlcNAcylation may mediate cardiac mechanical dysfunction in diabetes. However, a number of important points have remained uncertain, including whether this mechanism mediates the development of cardiomyopathy in the more clinically relevant condition of insulin-resistant (type 2) diabetes, and the relative importance of cellular UDP-GlcNAc concentration vs. OGT activity in mediating O-GlcNAcylation in the diabetic heart.

In their new work, Fülop and colleagues (8) report serial measurements of cardiac UDP-GlcNAc, O-GlcNAc-modified protein, and OGT expression, along with single-cell calcium transients and mechanical performance, during the transition from the insulin-resistant normoglycemic stage to the hyperglycemic stage in the Zucker diabetic fatty (ZDF) rat. This study represents an important extension of previous work, both in its comprehensive scope and in the attempt to characterize a rodent model of obesity and insulin resistance highly relevant to the increasingly prevalent form of human type 2 diabetes sometimes referred to as “diabetes.” The transition from normoglycemia to hyperglycemia in ZDF rats was found to be associated with cellular accumulation of UDP-GlcNAc and O-GlcNAc-modified protein, delayed calcium sequestration, and impaired mechanical relaxation. However, OGT expression was no different in hyperglycemic ZDF rats than in hearts of age-matched lean control rats, suggesting that protein O-GlcNAcylation in this model may be predominantly substrate driven and therefore presumably determined by the magnitude of cardiomyocyte HBP flux.

These observations demonstrate that increased cardiomyocyte HBP flux, with concomitantly increased protein O-GlcNAcylation, may contribute to the development of a specific cardiomyopathy in type 2 diabetes. Because both
excess glucose availability and excess fatty acid availability can theoretically increase cardiomyocyte HBP flux, this mechanism would be a potential candidate to mediate the effects of both “glucose toxicity” and “lipotoxicity” on the diabetic heart (15, 16). Correspondingly, the observations of Fulop et al. (8) suggest that strategies to inhibit entry of glucose carbon into the HBP, either directly (e.g., by inhibiting the rate-limiting enzyme glutamine:fructose-6-phosphate amidotransferase; GFAT) or indirectly (e.g., by lowering circulating fatty acid or glucose levels, or stimulating glycolysis and/or pyruvate oxidation), might prevent or reverse the development of diabetic cardiomyopathy by reducing the level of cardiomyocyte O-GlcNAcylation and therefore its functional consequences.

An interesting subsidiary observation of the current study of Fulop et al. (8) is that O-GlcNAcylation in the hearts of hyperglycemic ZDF rats appeared to be largely limited to a high-molecular-weight band of cardiomyocyte protein. Characterization of the specific high-molecular-weight protein(s) involved, for example, determining whether these include contractile proteins or calcium channels, seems likely to shed additional light on the precise mechanism by which elevated circulating levels of glucose and free fatty acids impair cardiac E-C coupling. Given the recognized difficulty of trying to maintain circulating glucose and fatty acid levels normal over long periods of time in obese patients with type 2 diabetes, a pharmacological therapy targeted to the actual O-GlcNAcylation event responsible for conferring diabetic cardiac mechanical dysfunction would have obvious attraction.

A number of important questions regarding the relationship between cardiomyocyte HBP flux and cardiac E-C coupling in diabetes remain to be answered. Among these are how insulin resistance and its attendant changes in substrate availability influence the expression or activities of the other enzymes involved, including perhaps most importantly GFAT and O-GlcNAcase; whether the relationships among cellular UDP-GlcNAc concentration, OGT expression, and O-GlcNAcylation are sensitive to ambient insulin level; and whether levels of heart O-GlcNAcylation continue to increase with increasing age in animals continuously exposed to a diabetic milieu. The ZDF rat, and other genetic models of obesity and insulin resistance, would seem a logical and potentially productive venue for the study of these questions.

REFERENCES