The Glycolytic Pathway to Coronary Heart Disease: A Hypothesis

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Coronary heart disease (CHD) is pathogenetically linked to numerous metabolic disturbances. These are inextricably interrelated, constituting identifiable clusters or syndromes of cardiovascular risk. Prominent among these is the insulin resistance syndrome, whose components, including hyperuricemia, have all been linked to CHD pathogenesis. Many mechanisms have been put forward to account for the emergence of this syndrome, but none offer a satisfactory explanation for the involvement of hyperuricemia. Possible explanations relate to the observation of glycolytic disturbances in insulin-resistant and hyperuricemic states. This might be expected from the fact that uric acid production is linked to glycolysis and that glycolysis is controlled by insulin. Phosphoribosylpyrophosphate (PPRP) is an important metabolite in this respect. Its availability depends on ribose-5-phosphate (R-5-P), the production of which is governed by glycolytic flux. Diversion of glycolytic intermediates toward R-5-P, PPRP, and uric acid will follow if there is diminished activity of glyceraldehyde-3-phosphate dehydrogenase (GA3PDH), which is regulated by insulin. Serum triglyceride concentrations may also increase, as might be expected from accumulation of glycerol-3-phosphate. Thus, intrinsic defects in GA3PDH and a loss of its responsiveness to insulin, by causing accumulation of glycolytic intermediates, may explain the association between insulin resistance, hyperuricemia, and hypertriglyceridemia. This scenario raises the possibility that disturbances of a single glycolytic enzyme may be pivotal in the modulation of metabolic risk factors for CHD.

THE CLASSIC CARDIOVASCULAR risk factors, such as age, obesity, hypertension, smoking, and hypercholesterolemia, only partly explain the incidence of coronary heart disease (CHD).[1] Increasing evidence indicates that other disturbances encompassing various aspects of metabolism also contribute to CHD pathogenesis. Such disturbances are inextricably interrelated, constituting identifiable groups of risk factors, or syndromes of cardiovascular risk. One such syndrome is the insulin resistance syndrome, which includes obesity, hypertension, non–insulin-dependent diabetes mellitus (NIDDM), hypertriglyceridemia, low high-density lipoprotein cholesterol, glucose intolerance, hyperinsulinemia, and insulin resistance as its core characteristics.[2] These metabolic disturbances have all been linked to the development of CHD. Importantly, insulin resistance, which plays a pivotal role in the coordination of the insulin resistance syndrome, has recently been shown to be independently related to atherosclerosis.[3]

Hyperuricemia has long been associated with CHD and with its risk factors, including obesity, hypertension, and NIDDM.[4-7] Increasing uric acid levels also correlate with the metabolic disturbances associated with these conditions: glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and dyslipidemia.[8-10] This clustering of hyperuricemia with other metabolic risk factors for CHD has justified the inclusion of increased uric acid levels in the panel of correlated risk factors that constitute the insulin resistance syndrome.[11,12] However, there is no satisfactory explanation for the involvement of hyperuricemia in CHD risk or in the insulin resistance syndrome. An inverse relationship between uric acid excretion and insulin concentration has been demonstrated in several studies,[5,13,14] and this has led to the supposition that impairment of renal elimination of uric acid is the sole contributor to elevations in serum uric acid levels in the insulin resistance syndrome. However, these studies have not measured uric acid production. In the absence of such measurements, the possibility that insulin resistance is linked to hyperuricemia through uric acid production cannot be excluded.

Uric acid production is linked to the cellular effects of insulin through glycolysis, the principal pathway of carbohydrate metabolism. Given that both insulin resistance and hyperuricemia are associated with glycolytic disturbances, it is tempting to speculate that the insulin resistance syndrome itself is coordinated at the glycolytic level. As well as accounting for the hyperuricemia of the insulin resistance syndrome, such a link may provide an important focus for insulin resistance itself and may account for a number of the other correlated disturbances of the syndrome, including hyperinsulinemia, impaired glucose tolerance, and hypertriglyceridemia. In the following review, we consider the possible importance of impairment in the action of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GA3PDH) in the emergence of the correlated disturbances of the insulin resistance syndrome.

SITES OF URATE PRODUCTION

In humans, uric acid forms a metabolic endpoint. The enzyme xanthine oxidoreductase (XO) catalyzes the formation of urate from xanthine, which is itself derived from the degradation of purine bases. The liver has traditionally been regarded as the major source of XO. However, more recent evidence indicates that XO is also present in peripheral tissues at greater than trace quantities. Urate production in skeletal muscle has been traditionally attributed to degradation of adenosine triphosphate (ATP), and it has recently been shown that XO is present in capillary endothelial cells and vascular smooth muscle cells of human skeletal muscle,[15] as well as the heart.[16] Accordingly, eccentric exercise in healthy human subjects leads to increased XO activity in microvascular endothelial cells of skeletal muscle, and this increase is associated with increases in plasma hypoxanthine levels.[17] Admittedly, reports on the presence of XO activity in the human heart have been conflicting. Despite the practical difficulties involved, there are several studies demonstrating that XO is present in the human heart.[16,18] This is

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consistent with the finding of coronary artery to coronary sinus gradients of uric acid concentrations in patients with chronic myocardial ischemia,[19] and with the finding of a net release of urate in the coronary sinus following coronary artery angioplasty in patients with CHD.[20] These data indicate that significant XO activity is present in both cardiac and skeletal muscle.

METABOLIC CONTROL OF URATE PRODUCTION

Production rates of uric acid are closely linked with purine production rates.[21] A key precursor in purine synthesis is the sugar ribose-5-phosphate (R-5-P), which is converted to phosphoribosylpyrophosphate (PPRP). The first step in de novo purine nucleotide synthesis is replacement of the pyrophosphate group of PPRP by the amide group of glutamine. This is the commitment and rate-limiting step of the pathway, and the amidotransferase enzyme responsible is under allosteric control by feedback inhibition from a variety of nucleotides. Importantly, the supply of PPRP can also control the rate of this critical step and can even overcome normal feedback control by nucleotide inhibition. Once the 5-phosphoribosyl amine has been formed, purine ring synthesis follows.

Clearly, the supply of PPRP is important in the control of purine and uric acid biosynthesis, and in turn will depend on the supply of R-5-P.[22] R-5-P is a component of the pentose phosphate pathway, and its levels depend on precursors supplied by the glycolytic pathway.[23] The importance of glycolytic intermediates in controlling R-5-P levels focuses attention on the relationship between glycolysis, the pentose phosphate pathway, purine metabolism, and uric acid. One branch point for diversion of glycolytic intermediates toward R-5-P and PPRP synthesis is controlled by the activity of the enzyme GA3PDH. Increased activity of this enzyme will result in continuing metabolism of glycolytic intermediates toward pyruvate. Diminished activity will result in diversion of glycolytic intermediates in the direction of PPRP, purine, and uric acid synthesis.

GA3PDH is a key enzyme of the glycolytic pathway and is responsible for the conversion of glyceraldehyde-3-phosphate (G3P) to 1,3biphosphoglycerate. Under normal physiological conditions, fructose biphosphate is converted to dihydroxyacetone phosphate (DHAP) and G3P, but the latter is readily converted to DHAP via triose phosphate isomerase. Under conditions of equilibrium, as much as 96% of the triose phosphate is DHAP. When GA3PDH activity is increased, the equilibrium shifts in favor of formation of G3P such that glycolysis may proceed to 1,3biphosphoglycerate (Fig 1).

The activity of GA3PDH is tightly regulated by insulin.[24,25] The gene for the enzyme contains the recently described positive insulin response element.[26] This allows insulin to drive glycolysis toward pyruvate production. Intrinsic defects in GA3PDH with regard to its activity, activation, or induction would be accompanied by a loss of responsiveness of the glycolytic pathway to insulin and possibly resistance to insulin-dependent cellular uptake of glucose. Alternatively, defective insulin action, resulting, for example, from low insulin levels, or impairment in insulin receptor activity or postreceptor insulin signaling could be associated with diminished GA3PDH activity. Thus, defective GA3PDH activity could cause or be the result of an insulin-resistant state. Either way, impairment of GA3PDH activity will be an important modulator of the metabolic effects of insulin resistance or insulin deficiency. The possibility that increased uric acid production could result from impaired GA3PDH activity has already been mentioned, and it should be evident that the link between increased uric acid levels and insulin resistance could be mediated by impairment of GA3PDH activity. GA3PDH activity has yet to be measured in studies with accompanying measurements of insulin resistance and uric acid metabolism. Nevertheless, there is strong support for these associations from experimental studies of the effects of GA3PDH inhibition, and from studies of conditions in which uric acid levels are increased.

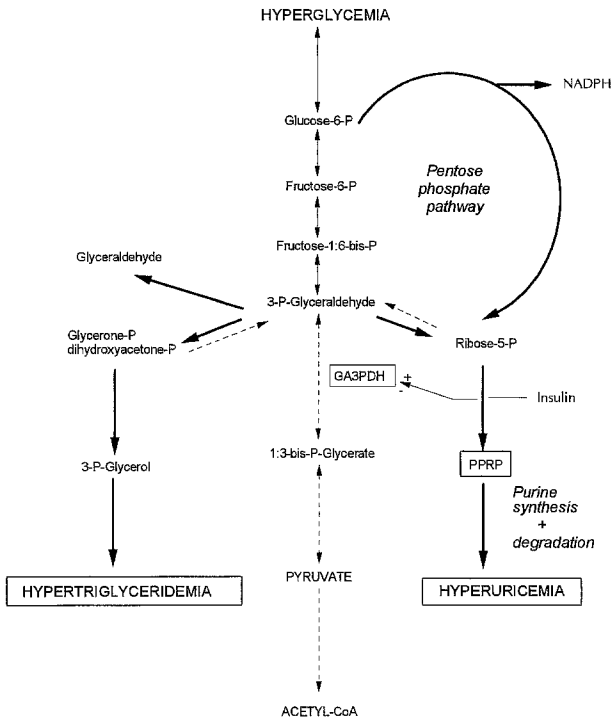

Fig 1. Possible consequences of decreased activity of GA3PDH. P, phosphate; CoA, coenzyme A.

EVIDENCE FOR THE IMPORTANCE OF LOW GA3PDH ACTIVITY IN HYPERURICEMIA

Studies on the effects of the polyol molecule, xylitol, provide an important insight into the relationship between glycolysis and uric acid production. It has long been recognized that ATP-depleting compounds such as xylitol cause marked increases in ATP degradation and uric acid production and hyperuricemia in vivo.[27,28] It was originally suggested that the mechanism by which xylitol decreases cellular ATP is through rapid phosphorylation of the polyol molecule. Although this certainly occurs and contributes to initial cellular ATP depletion, more recent studies have shown that xylitol inhibits glycolysis at the level of GA3PDH. This has the effect of blocking glycolytic NADH generation. Because the xylitol-induced block in glycolysis diminishes the synthesis of pyruvate, this further reduces cellular NADH production by decreas-

ing the amount of acetyl coenzyme A formed and slowing the flux of metabolites into the citric acid cycle.

$$3ADP + 3Pi + \tfrac{1}{2}O_2 + NADH + H^+ \rightarrow 3ATP + 4H_2O + NAD^+$$

If one considers the above equation for the synthesis of ATP, it becomes clear that limitations in the availability of NADH can significantly diminish cellular ATP synthesis. This is clear from the data of Vincent et al,[29] who showed that despite restoration of Pi 20 minutes following administration of xylitol to rat hepatocytes coupled to rapid increases in R-5-P and PPRP, cellular ATP remained depleted during all measured time points. This finding is important because it demonstrates that a compound, now known to block GA3PDH and cause cellular increases in DHAP and G3P,[27] leads to immediate increases in R-5-P and subsequent increases in PPRP. The fact that ATP is consistently depleted by xylitol further stimulates the flow of intermediates into purine metabolism. Following restoration of Pi, a stimulator of PPRP synthetase, this flux is increased further.

In accord with these in vitro studies, in vivo studies have associated xylitol administration with increases in serum concentrations of DHAP, G3P, and fructose biphosphate and decreases in pyruvate.[30] As would be expected from the impaired activity of GA3PDH, xylitol produces accumulation of R-5-P and increased availability of purine bases[30] and PPRP. The evidence therefore suggests that depletion of cellular ATP, mediated partly through inhibition of glycolysis at the level of GA3PDH, is a potent mechanism through which uric acid production may be increased by xylitol.

GA3PDH catalyzes the only oxidative step in glycolysis, with its conversion of G3P to 1,3-diphosphoglycerate. Therefore, studies of oxidative and nonoxidative glycolysis can provide insight into defects in GA3PDH activity. Del Prato et al,[31] in a series of glycemic clamp studies, noted that when blood glucose levels were normalized by continuous infusion of insulin in patients with NIDDM, there was increased nonoxidative glycolysis and lipid oxidation compared with controls. However, net glycolysis, glucose oxidation, and glycogen synthesis were all reduced. Increasing the clamped glucose level without a concomitant increase in insulin resulted in normalization of the rate of glucose uptake and net glycolysis and an increase in glycogen deposition, but nonoxidative glycolysis and lipid oxidation remained higher and glucose oxidation lower. Increasing the clamped glucose level with a concomitant increase in insulin was associated with normalization of the rate of glucose uptake, net glycolysis, glycogen formation, and lipid oxidation, but nonoxidative glycolysis remained elevated and glucose oxidation reduced. Similar findings were reported by Vaag et al.[32] Therefore, although marked hyperinsulinemia normalizes glycogen synthesis and total glycolytic flux, it does not restore a normal distribution between nonoxidative glycolysis and oxidative glycolysis. Since GA3PDH catalyzes the first and only oxidative step in the glycolytic pathway, these findings point to a critical defect in patients with NIDDM at the level of GA3PDH. There is considerable evidence in support of reduced GA3PDH activity in patients with NIDDM[33-36] and in animal models of diabetes mellitus.[37,38] Insulin resistance and elevated uric acid levels predict the development of NIDDM, and patients with NIDDM are characterized by both of these metabolic disturbances.

Defects in the activity of GA3PDH in patients with NIDDM might be expected to result in accumulation of early intermediates in the glycolytic pathway. It is noteworthy that, rather than glucose, the principal sugars involved in nonenzymatic glycosylation of proteins in patients with NIDDM are the early intermediates in glycolysis, G6P, fructose-6-phosphate, and G3P.[39]

To the extent that insulin stimulates GA3PDH activity, NIDDM—a condition defined by defective insulin action—will be expected to be associated with defective GA3PDH activity. Equally, primary defects in the structure of GA3PDH might be expected to result in a defective glycolytic response to insulin, and there is evidence that a diminished activity of GA3PDH can arise from diminished activities of genetic variants[40] and from differences in posttranslational modification of its isoenzymes.[41] As yet, there is insufficient evidence to determine the extent to which primary defects in insulin action or in GA3PDH structure contribute to the etiology of disturbances in carbohydrate metabolism in humans. However, variations in insulin action or insulin responsiveness may not be the only factors contributing to defective GA3PDH activity in NIDDM. The plasma of patients with NIDDM has a significant GA3PDH-inhibitory effect, which has been attributed to a variety of substances. The growth hormone–derived peptide fragment somantin is one possible candidate.[42,43] Schwartz and Turfus[44] attributed the GA3PDH-inhibitory effect to a low–molecular-weight nonpeptide material, which was not somantin. Terato et al[45] also found a similar GA3PDH-inhibitory activity in the urine of diabetic patients, attributing it to a low–molecular-weight substance.[45] Recently, endogenous aldehydes found in the serum of diabetic patients and rats have been shown to exert a potent, noncompetitive inhibitory effect on GA3PDH.[46]

Although much of the evidence for the importance of GA3PDH comes from studies of diabetes, there is some evidence from other insulin-resistant states. Ferrannini et al[47] have shown that insulin-resistant hypertensive patients have a defect of nonoxidative glucose metabolism similar to that observed in patients with NIDDM. The reduced rate of nonoxidative glucose disposal (glycolysis and glycogen synthesis) appeared to account for virtually all of the defect in glucose uptake. When insulin-resistant monkeys are subjected to insulin-stimulated conditions, there is accumulation of G6P, suggesting a glycolytic pathway defect distal to this metabolite.[37]

The emerging picture therefore is that impaired GA3PDH activity in insulin-resistant states, including NIDDM, hypertension, and obesity, results in accumulation of proximal glycolytic intermediates and their diversion along alternative routes. This accounts for the consistent observation in states of insulin-resistance of impaired oxidative glucose disposal and increased uric acid levels.

EVIDENCE FOR THE IMPORTANCE OF LOW GA3PDH ACTIVITY IN HYPERTRIGLYCERIDEMIA

As already described, the metabolic effects of xylitol provide strong supportive evidence for a link between impaired GA3PDH

activity and increased uric acid synthesis. Xylitol infusion is also associated with increased triglyceride levels.[48,49] One aspect of glycolytic metabolism could link impaired GA3PDH activity with triglyceride synthesis. An increased availability of DHAP will result in increased availability of glycerol-3-phosphate,[50,51] one of the primary precursors in triglyceride synthesis. Increased activity of glycerol-3-phosphate dehydrogenase—the enzyme responsible for conversion of DHAP to glycerol-3-phosphate—and increased triglyceride synthesis have been observed in obesity[52,53] and in differentiating rat preadipocytes.[54] The importance of the pentose phosphate cycle is suggested by findings relating to streptozotocin-induced diabetes, in which there is hypertriglyceridemia,[55] accumulation of R-5-P, a striking increase in the activity of the pentose phosphate cycle,[56] and a marked reduction of GA3PDH activity. An increased activity of the pentose phosphate pathway enzyme glucose-6-phosphate dehydrogenase (G6PDH) has been reported in hypertensive patients and their siblings.[57,58] Increased activity of G6PDH has also been reported in striated muscle of patients with NIDDM,[35] and in animal models of insulin resistance[59] and of hypertension. These results strongly suggest an increased activity of the pentose phosphate pathway coinciding with reduced oxidative metabolism. It is also noteworthy that increased activity of G6PDH in the pentose phosphate pathway results in increased availability of NADPH, essential for the synthesis of fatty acids.

The concept that uric acid and triglyceride metabolism can, under certain conditions, be linked to a common metabolic pathway is suggested by the consistent association of hypertriglyceridemia and hyperuricemia both in healthy individuals and in those with insulin resistance. In addition, fructose, which is known to cause impaired glucose tolerance, hyperinsulinemia, and insulin resistance,[60] also produces hypertriglyceridemia and hyperuricemia both in healthy subjects[61,62] and in patients with fructose intolerance.[63,64] Long-term absorption of fructose has been shown to lead to adaptations that diminish glucose tolerance and produce hyperinsulinemia, increased lipogenesis, and a resultant increase in very–low-density lipoprotein production and hypertriglyceridemia.[65] Pentose phosphate pathway activity and triglyceride synthesis are increased in diabetes,[66] hypertension, hyperinsulinemia,[59] and obesity.[53,67,68] Inborn errors of metabolism are also associated with hyperuricemia and hypertriglyceridemia: fructose 1,6-diphosphatase deficiency,[69] associated with accumulation of glycolytic intermediates,[70] causes elevated triglyceride and uric acid levels. It is also noteworthy that there is a significant correlation between uric acid production and serum triglyceride levels in patients with primary gout,[71-74] and it has been suggested that an increased flux of glycolytic intermediates through the pentose phosphate pathway may represent a key step in jointly increasing the levels of both of these metabolites.[73]

CONCLUSIONS

The possibility that variation in the activity of the enzyme GA3PDH might be responsible for the coordination of the metabolic disturbances that cluster with hyperuricemia does not appear to have been addressed before. As a consequence, the possibility has not been rigorously tested, and much of the evidence we present here is derived from studies designed to address other issues. Nevertheless, a remarkably consistent picture emerges according to which insulin resistance, hyperuricemia, and hypertriglyceridemia can be linked via disturbances in the activity of a single enzyme. These associations suggest an involvement of GA3PDH in the broader issue of the etiology of the insulin resistance syndrome, which has insulin resistance as its primary feature and includes hyperuricemia and hypertriglyceridemia among its core characteristics.

Speculatively, the associations described herein raise the possibility that glycolytic disturbances may be at the root of CHD pathogenesis. Further investigations on the possible relationships between variations in GA3PDH activity and CHD risk could include a more rigorous evaluation of the "metabolic signature" for reduced GA3PDH activity in insulin-resistant states. This signature will include increased uric acid concentrations, increased fatty acid synthesis and triglyceride levels, increased pentose phosphate shunt activity, and decreased oxidative energy availability. These disturbances may be sought in situations in which glycolytic metabolism has been disrupted by external agents or in established clinical conditions.

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