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The Cellular Fate of Glucose and Its Relevance in Type 2 Diabetes

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Type 2 diabetes is a complex disorder with diminished insulin secretion and insulin action contributing to the hyperglycemia and wide range of metabolic defects that underlie the disease. The contribution of glucose metabolic pathways *per se* in the pathogenesis of the disease remains unclear. The cellular fate of glucose begins with glucose transport and phosphorylation. Subsequent pathways of glucose utilization include aerobic and anaerobic glycolysis, glycogen formation, and conversion to other intermediates in the hexose phosphate or hexosamine biosynthesis pathways. Abnormalities in each pathway may occur in diabetic subjects; however, it is unclear whether perturbations in these may lead to diabetes or are a consequence of the multiple metabolic abnormalities found in the disease. This review is focused on the cellular fate of glucose and relevance to human type 2 diabetes. (*Endocrine Reviews* 25: 807–830, 2004)

I. Introduction

THE PATHOPHYSIOLOGY OF type 2 diabetes involves impairments in both insulin action and insulin secretion (1–3). Insulin sensitivity is determined by the ability of insulin to promote glucose uptake and utilization. Thus, in insulin-resistant conditions, there is decreased glucose clearance in response to insulin. Insulin regulates glucose homeostasis primarily through suppression of hepatic glucose production and stimulation of peripheral (and to a lesser degree, splanchnic) glucose uptake (4). Clinical studies in man have demonstrated impaired ability of insulin to promote glucose clearance in type 2 diabetic subjects assessed after oral glucose administration (5), during euglycemic hyperinsulinemic clamp studies (6), or by nuclear magnetic resonance spectrometry (7). The most conclusive evidence for defective insulin sensitivity in type 2 diabetes comes from euglycemic hyperinsulinemic clamp studies, in which total body glucose clearance is shown to be reduced in type 2 diabetic subjects compared with age and weight-matched controls (6). Furthermore, *in vivo* human studies suggest that the primary site of reduced insulin-mediated glucose uptake is located in the peripheral (muscle) tissue (6, 8). Decreased insulin-mediated glucose clearance seen in type 2 diabetes has also been demonstrated in humans at risk for development of diabetes, including persons with obesity, hypertension, hyperlipidemia, or a strong family history of disease (9, 10). Thus, extensive research on the development of type 2 diabetes has been focused on cellular and molecular processes of insulin signaling (11, 12).

In humans, insulin secretion increases with progressive insulin resistance, and the relationship is both hyperbolic and tightly coupled (13). Failure of pancreatic β-cells to compensate for insulin resistance is critical in the pathogenesis of type 2 diabetes (4). Factors limiting the ability of β-cells to respond to an increasing demand remain largely unknown, but likely involve genetic factors as well as glucotoxicity and lipotoxicity (14, 15). In addition, diminished insulin secretion could be mediated in part by abnormal glucose metabolism within the β-cell where glucose metabolism is coupled to insulin biosynthesis and secretion (16), as well as to β-cell mass by hypertrophy, hyperplasia, and neogenesis (17). Moreover, recent studies have shown the β-cell itself to be an insulin-responsive tissue, demonstrating an additional potential link between peripheral insulin resistance and β-cell failure (18, 19).

Glucose metabolic pathways must also be considered in the pathogenesis of the disease. Whole body glucose clearance is due to both insulin-dependent and insulin-indepen-

Abbreviations: AMPK, AMP-activated protein kinase; CoA, coenzyme A; fructose-6-P, fructose-6-phosphate; G-6-P, glucose 6-phosphate; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GFAT, glutamine fructose-6-P amidotransferase; GLUT, glucose transporter; GSK, glycogen synthase kinase; K_m, Michaelis-Menten constant; MODY, maturity onset diabetes of the young; NADH, nicotinamide adenine dinucleotide; PDK, pyruvate dehydrogenase kinase; PGC-1α, PPARγ coactivator 1α; PI3K, phosphatidylinositol-3-kinase; PKA, protein kinase A; PKC, protein kinase C; PP1, protein phosphatase-1; PPAR, peroxisome proliferator-activated receptor; S_G, glucose effectiveness; SGLT, sodium-glucose cotransporter; UDP, uridine diphosphate.

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dent mechanisms, with insulin-independent clearance derived from the ability of plasma glucose to influence its own clearance by a mass action effect (20–23). In addition, glucose *per se* may play an important role in promoting glucose resistance via down-regulation of the enzymes involved its own metabolism, such as AMP-activated protein kinase (AMPK) (24), permitting amplification of diminished clearance. Thus, in definition, glucose resistance would exist *in vivo* when for any reason insulin-independent glucose clearance is low. Insulin-independent glucose clearance is a major determinant of iv glucose tolerance in healthy subjects (25), such that after glucose administration, as much as half of the decline in plasma glucose is due to the effect of hyperglycemia on glucose disposal (26). To date, the glucose effectiveness (S_G) measure from the Bergman model iv glucose tolerance test remains one of the best measures of glucose resistance (21). It should be noted that S_G derived from the iv glucose tolerance testing model maintains a dependence on basal insulin and is thus a mixed parameter. In people with diabetes, the ability of glucose to promote glucose clearance is impaired, suggesting glucose resistance (27). Diminished insulin-independent glucose clearance is seen early in the pathogenesis of type 2 diabetes, as demonstrated by the contribution of glucose resistance to the incidence of disease in the prospective evaluation of the development of diabetes in normoglycemic offspring of type 2 diabetic parents (10). Thus, in addition to the established role of insulin in the pathophysiology of diabetes, glucose itself plays a central role through its ability to control insulin secretion and to self-regulate its own disposal.

However, the minimal model has been suggested to systematically overestimate S_G in the presence of rapidly fluctuating glucose and insulin concentrations as seen during the iv glucose tolerance testing conditions (28) or underestimate S_G in the presence of blunted insulin secretory capacity (29). To overcome these limitations, others have employed clamp techniques in which basal insulin concentrations were maintained constant by an exogenous insulin infusion, endogenous hormone secretion was inhibited by somatostatin, and assessment was made of the integrated glycemic response above baseline during identical prandial glucose infusions as a measure of S_G at basal insulin (30). In this important study, diminished S_G was found to be mediated by a reduced ability of glucose to stimulate its own disappearance via mass action and by an inhibitory effect of glucose on its own clearance. Both factors contributed to the greater rise in glucose in diabetic subjects, and this occurred without altered suppression of endogenous glucose production. Such studies provide additional support that in the presence of basal insulin concentrations, the effects of glucose *per se* on its own metabolism are diminished in people with type 2 diabetes.

To better understand the role of glucose resistance in the development of diabetes, this review will focus on the different pathways of glucose metabolism, their contribution to the development of type 2 diabetes, and the potential targets of antiglycemic drugs. In the attempt to understand the underlying pathophysiology of type 2 diabetes and to develop new therapeutic agents to treat the disease, the scientific community is actively performing investigations that involve increasing or decreasing levels or activity of proteins in these glucose metabolic pathways using site-directed mutagenesis, knock-in/knockout models, or gene silencing techniques singly or in combination, in cell and animal models. These studies reveal both specificity of enzyme function and a surprising degree of redundancy by which pathway function can be maintained even in the setting of specific perturbations. Traditionally, metabolic pathway activity has been considered to be regulated by either substrate availability or rate-limiting enzymes. However, it is becoming increasingly apparent that activity of entire pathways can be regulated in a coordinated fashion at the level of protein–protein interactions (exemplified by glycogen synthase and phosphorylase activities) or at the transcriptional level by nuclear factor(s) and cofactor(s) such as those seen with peroxisome proliferator-activated receptor (PPAR)γ coactivator 1α (PGC-1α). Changes in expression or activity of single gene products may not appear significant independently, but small alterations in multiple steps of a pathway may exist simultaneously with substantial physiological implications. Although there is a large body of literature on insulin resistance contributing to the hyperglycemia of type 2 diabetes (reviewed in Refs. 2 and 31) and on the potential role of primary disturbances in lipid metabolism contributing to secondary changes in carbohydrate metabolism in diabetes and other insulin-resistant states (reviewed in Refs. 32 and 33), formal discussion of these topics is beyond the scope of this review. Rather, this review will focus on the clinical defects that occur in carbohydrate metabolism in type 2 diabetes, both physiological and genetic, and on pharmacological interventions that may ameliorate these defects as a framework to better understand the contribution of the cellular fate of glucose to the development of type 2 diabetes.

II. The First Step: Glucose Transport and Phosphorylation

A. Glucose transport pathways

Although there are three principal monosaccharides resulting from the digestive process, *i.e.*, glucose, fructose, and galactose, both fructose and galactose are readily converted to glucose by the liver; thus, for all these sugars, glucose metabolism becomes a critical factor in determining their fate. Although fatty acids and ketone bodies can be used for fuel in muscle and other tissues in the fasted state, in mammalian cells glucose metabolism generating ATP through either aerobic or anaerobic pathways provides the principal source of cellular energy and substrate storage (Fig. 1). However, due to its hydrophilic nature, glucose cannot penetrate the lipid bilayer, and thus, specific transporter proteins are required for facilitated diffusion into cells. The energy-independent transport of glucose down its concentration gradient is mediated by two distinct families of hexose transport proteins present on the cell membrane (34): facilitative glucose carriers [(glucose transporters (GLUTs)] and sodium-glucose cotransporters (SGLTs).

1. Facilitative GLUT family. To date, 13 functional mammalian facilitated hexose carriers (GLUTs) have been characterized by molecular cloning. Structurally, all members of this family

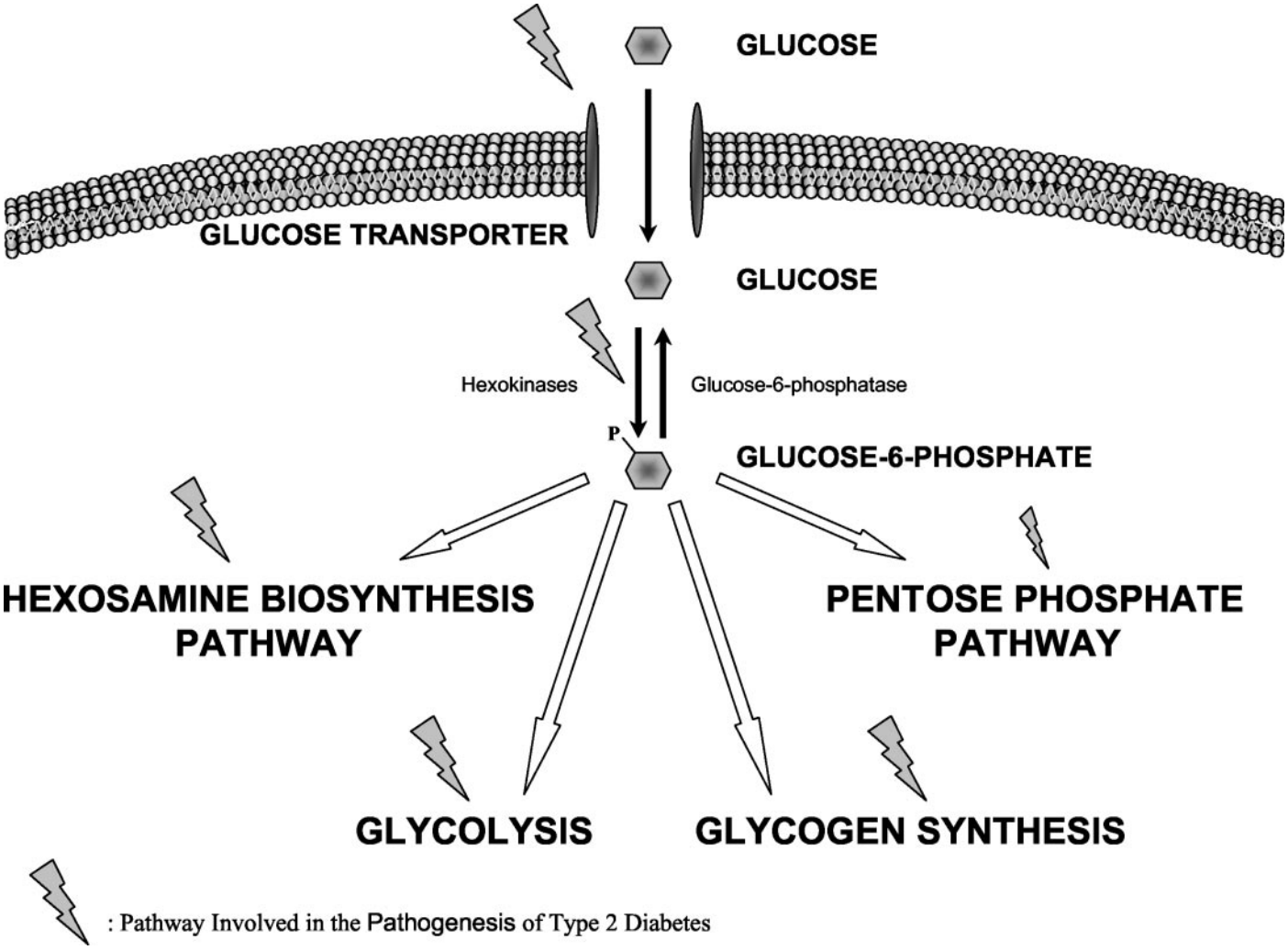

FIG. 1. Schematic representation of the cellular fate of glucose showing the major metabolic pathways: glucose transport and phosphorylation, glycolysis, glycogen synthesis, pentose phosphate pathway, and hexosamine biosynthesis pathway.

of proteins possess 12 membrane-spanning helices, with a larger intracellular loop connecting the sixth and seventh helices. The facilitated transport of glucose is saturable, stereoselective, and bidirectional. According to the sequence similarities, three classes of GLUTs have been defined. Class I GLUTs include the high-affinity binding proteins GLUT1, GLUT3, and GLUT4 and the lower-affinity transporter GLUT2. Class II transporters including GLUT5, GLUT7, GLUT9, and GLUT11 or myoinositol transporter (HMIT1) have a very low affinity for glucose and preferentially transport fructose, and thus they are not additionally discussed in this review. Class III transporters comprise four novel GLUTs, GLUT6, GLUT8, GLUT10, and GLUT12 (35).

a. Class I: high-affinity transporters (GLUT1, GLUT3, and GLUT4). The Michaelis-Menten constants (K_m) of most of the class I GLUTs (between 2 and 5 mmol/liter) are below the normal range of blood glucose concentrations. Thus, the high-affinity transporters function at rates close to maximal velocity, and levels of cell surface expression greatly influence the rate of glucose uptake into cells.

i. GLUT1. In adult tissues, GLUT1 is expressed at the highest levels in erythrocytes, kidney, colon, and cells of blood-tissue barriers, including glial cells of the blood-brain barrier. GLUT1 is also present at low levels in liver, adipose tissue, and muscle. GLUT1 is the primary GLUT in fetal tissues and tissue culture cells (34).

GLUT1 is a widely expressed isoform that provides glucose transport under basal conditions for many cells. Moreover, the exposure of many mammalian cell types to metabolic stresses such as hypoxemia and inhibition of oxidative phosphorylation or to osmotic stresses results in an acute increase in the rate of glucose uptake by GLUT1, probably mediated by AMPK (36). This adaptive response allows cells to increase their ATP levels when necessary from the glycolytic pathway. The activity of GLUT1 is modulated by pretranslational modifications of gene expression (37), by posttranslational modifications including transporter redistribution mediated by insulin in insulin-sensitive tissues (38), and by increased substrate binding activity probably via protein–protein interactions (39).

Two different hemizygous nonsense mutations of the GLUT1 gene resulting in truncated protein expression have been described in man (40). These patients have a syndrome characterized by infantile seizures, delayed development, and microcephaly, with hypoglycorrachia (low cerebrospinal fluid glucose), but normal blood glucose.

ii. GLUT3. GLUT3 is the major neuronal GLUT isoform. With the lowest K_m for glucose, it is the ideal GLUT for neuronal cells that are incapable of glycogen storage yet have a high glucose demand (34). GLUT3 is also expressed in macrophages, platelets, placenta, and testes. The regulation of glucose uptake by GLUT3 occurs through cellular translocation (41) and regulation of gene expression by hyperglycemia (42). Dysfunction or inadequate expression of GLUT3 has not yet been described in man.

iii. GLUT4. GLUT4 mediates insulin-stimulated glucose uptake by skeletal muscle, heart, and white and brown adipose tissues by a mechanism involving translocation between cellular compartments. GLUT4 recycles continuously between the cell surface and the intracellular storage compartment. Insulin increases cell surface expression levels of GLUT4 by increasing the rate of externalization and reducing the rate of internalization (43). Thus, under hyperinsulinemic conditions, increased glucose entry into the muscle is due to the greater number of functioning GLUTs at the cell membrane (44). Although the mechanism of movement of GLUT4 to the cell surface differs, exercise can also increase external membrane GLUT4 levels, thereby facilitating increased glucose disposal (44).

The fundamental role of GLUT4 in glucose homeostasis can be demonstrated in transgenic animal models. Muscle-specific overexpression of GLUT4 is sufficient to significantly improve insulin action and to reduce blood glucose levels in diabetic mice (45, 46). Overexpression of GLUT4 in adipose tissue improves glucose tolerance and induces fat cell hyperplasia (47). Conversely, targeted disruption of GLUT4 in muscle causes both reduced basal glucose transport and a near-absence of stimulation by insulin or muscle contraction, as well as whole-body insulin resistance and glucose intolerance from an early age (48). The phenotype of the muscle-selective disruption of GLUT4 contrasts with that of the whole-body GLUT4 knockout mouse, which exhibits growth retardation, severely reduced adipose tissue deposits, cardiac hypertrophy, and decreased life span (49). These GLUT4-null mice have decreased insulin-stimulated skeletal muscle glucose uptake and impaired insulin tolerance (49, 50). Although the cause of the phenotypic differences between selective tissue and whole-body deficiency of GLUT4 remains unclear, it is possible that compensatory overexpression of other GLUTs, as well as indirect effects of GLUT4 on fat storage and metabolism, may explain the disparity in insulin tolerance between these models.

b. Class I: low-affinity transporters (GLUT2). GLUT2 is present on β-cells and in tissues exposed to large glucose fluxes, such as intestine, liver, and kidney (51). GLUT2 has a high transport capacity and a higher K_m for glucose than GLUT1 ($K_m \approx 25$, compared with 6 mmol for glucose, GLUT2 *vs.* GLUT1, respectively) (52, 53). Thus, the rate of transport of glucose by GLUT2 is largely proportional to the ambient glucose concentration, a feature that allows for glucose sensing at times where levels of glucose change, as in the postprandial state. Hyperglycemia induces GLUT2 gene expression in pancreatic islets and in the liver, whereas hyperinsulinemia decreases GLUT2 in the liver (54–56). The pancreatic β-cells of GLUT2-null mice are characterized by a loss of first phase but preserved second phase insulin secretion (57). In humans, an inactivating mutation of GLUT2 is present in Fanconi-Bickel syndrome, a rare autosomal recessive disorder of carbohydrate metabolism, characterized by fasting hypoglycemia, hepatorenal glycogen accumulation, glucose and galactose intolerance, and a characteristic proximal tubular nephropathy (58, 59). Although most studies suggest that glucokinase enzymatic activity is rate limiting for the liver and β-cell (reviewed in Ref. 60), expressions of both GLUT2 and glucokinase appear to have coordinate regulation (54, 61), causing controversy as to whether it is transport or phosphorylation that limits pathway activity in diabetes (57, 62).

c. Class III: novel GLUTs (GLUT6, GLUT8, GLUT10, and GLUT12). Less is known about the Class III transporter proteins. They exhibit tissue- and cell-specific expression patterns and demonstrate preferential transport of glucose similar to class I transporters. GLUT6 (previously named GLUT9) is predominantly expressed in spleen, leukocytes, and brain (63). It undergoes tightly regulated subcellular redistribution in response to an unknown stimulus (64). In humans, GLUT8 (previously named GLUTX1) is predominantly found in insulin-sensitive tissues such as muscle, fat, and liver, as well as in testis, and is inhibited by fructose (65). GLUT10 is predominantly expressed in insulin-sensitive tissues (liver, muscle, and pancreas), but is also found in lung, brain, placenta, and kidney (66). Likewise, GLUT12 is predominantly expressed in skeletal muscle, heart, fat, and prostate. In the absence of insulin, this receptor is found in a perinuclear location (67). To date, there are no known human or animal diseases associated with alterations in either protein structure or expression of the class III transporters.

2. SGLT family. Members of this family of transporters structurally contain 14 transmembrane α-helices. Sodium permeates through the NH_2-terminal of the protein, and the sugar via the COOH-terminal (68). These proteins are expressed at the highest levels in the intestine and kidney. Two distinct members of the SGLT family have been described; however, cDNA library data suggest the existence of additional GLUTs, which have yet to be characterized in detail (68).

a. SGLT isoform-1 (SGLT1). SGLT1 utilizes the electrochemical sodium gradient to transport glucose and galactose against their concentration gradients, although it can also act bidirectionally (68). SGLT1 is responsible for the dietary uptake of glucose and galactose from the lumen of the small intestine and plays a minor role in reabsorption from the urine in the nephron. A defect in SGLT1 has been implicated in glucose-galactose malabsorption, a syndrome of neonatal diarrhea that can result in death unless these sugars are removed from the diet (69).

b. SGLT isoform-2 (SGLT2). SGLT2 is principally expressed in the kidney, and it preferentially transports glucose across the brush border of the human proximal tubule. Changes in sodium or glucose filtration rates modulate the expression of SGLT2 in renal proximal tubular cells (70). The major portion of the filtered glucose is reabsorbed in the early proximal tubule by SGLT2. Recently, a nonsense mutation of SGLT2 was implicated in a case of autosomal recessive renal glycosuria (71).

3. Role of an abnormal glucose transport in human type 2 diabetes. Muscle is the principal site of insulin-stimulated glucose disposal *in vivo*. Previous studies have indicated that in muscle, glucose transport is the rate-limiting step for glucose metabolism in normal glucose-tolerant (72, 73) and diabetic (74, 75) persons. Defects in total glucose transport into muscle have been implicated in the reduced insulin sensitivity observed in type 2 diabetes. Glucose transport activity, assessed by serial measurements of intracellular glucose using a ^{13}C-nuclear magnetic resonance technique, appears to be the rate-controlling step in insulin-stimulated muscle glycogen synthesis in type 2 diabetic patients (76). Moreover, insulin-resistant offspring of parents with type 2 diabetes manifest a similar defect (77).

Of all the transport proteins, GLUT4 has been most extensively studied in humans with insulin resistance. In the muscle of these subjects, there appears to be normal expression of GLUT4 but diminished targeting and trafficking (78–80). Such alterations in protein regulation are also seen in adipocytes (81), and these cells similarly have a marked reduction in GLUT4 expression in type 2 diabetes (82). Polymorphisms in the GLUT4 gene are very rare in type 2 diabetes and have the same prevalence among nondiabetic persons, suggesting that these are population variants and do not play a role in the etiology of the disease (83). Exercise, in part by inducing stimulation of GLUT4 translocation, has a therapeutic effect on control of glycemia in people with diabetes (84) and decreases the risk for type 2 diabetes in high-risk populations (85), although it may not be appropriate for patients with extremely poor glycemic control (86) or those with significant underlying cardiovascular disease. AMPK increases GLUT4 translocation in response to insulin and during exercise by insulin independent mechanisms (84).

GLUT10 may also contribute to the decreased glucose transport seen in type 2 diabetes and was identified through a survey of expressed sequences in the type 2 diabetes-linked region of human chromosome 20q12–13.1. The gene localization and functional properties suggest a role for GLUT10 in glucose metabolism and type 2 diabetes; however, the information available to date remains limited (66, 87). In addition, polymorphisms in the coding region of GLUT2 may be more abundant in persons with type 2 diabetes, although their effect on protein abundance and function requires further evaluation (88).

Increased concentrations of GLUTs would provide a therapeutic advantage in diabetes. Although the main therapeutic effect of sulfonylureas is to potentiate insulin secretion, some studies suggest an additional role of facilitating the translocation of both GLUT4 and GLUT1 to the cell surface in insulin-resistant adipocytes (89) and in myofibrils (90). Similarly, large doses of biguanides *in vitro* have demonstrated an ability to increase GLUT4 translocation in adipocytes (91) and in muscle (92). However, this effect has been harder to demonstrate *in vivo* (93). In isolated rat skeletal muscle, metformin stimulates glucose uptake coincident with AMPK activation (94), suggesting an important role of this signaling pathway in the regulation of glucose transport and drug effect. In contrast, thiazolidinediones, the newest class of insulin-sensitizing drugs, increase glucose disposal in peripheral tissues (93, 95), and *in vitro* studies confirm that thiazolidinediones are able to enhance both GLUT1 expression (96, 97) in cultured muscle and mesangial cells and GLUT4 translocation in muscle (98). These effects on glucose transport also appear to be mediated through activation of AMPK, although signaling pathways distinct from those of metformin are involved (99). These *in vitro* findings are supported *in vivo* by studies of troglitazone in type 2 diabetic humans, which demonstrate improved insulin responsiveness in skeletal muscle and increased glucose transport activity, as assessed by euglycemic hyperinsulinemic clamp and nuclear magnetic resonance and spectrometry (100, 101).

B. Phosphorylation/dephosphorylation of glucose

1. Description of the pathways. The first step in glucose metabolism is its transport into cells where it is rapidly phosphorylated to glucose 6-phosphate (G-6-P) by hexokinases, trapping the glucose within the cell. The reverse reaction is mediated by the enzyme glucose 6-phosphatase.

a. Hexokinase family. Mammalian tissues contain four types of hexokinases, designated as hexokinases I-IV depending on their electrophoretic mobility. These isozymes also differ in their regulatory properties, tissue distribution, and intracellular location. The type I-III isozymes have a molecular mass of approximately 100 kDa and are thought to have evolved by duplication and fusion of a gene encoding an ancestral 50-kDa hexokinase. The type IV isozyme is about 50 kDa and is presumed to have evolved directly from the ancestral gene. As expected from this proposed evolutionary scenario, the isozymes exhibit striking internal sequence similarity, with the N- and C-terminal halves being approximately 50% identical (102). Hexokinases I-III have a low K_m (10^{-6} to 10^{-1} mmol/liter), whereas hexokinase IV, also named glucokinase, has a high K_m (between 6 and 15 mmol/liter) for glucose.

i. High-affinity hexokinases (types I, II, and III). Hexokinases I-III all exhibit high affinity for glucose. These proteins are subject to varying degrees of feedback inhibition by their product G-6-P.

Hexokinase I is relatively ubiquitous, is found in skeletal muscle and β-cells, but has the highest levels of expression in brain and kidney (103). A significant portion is associated with mitochondria. The mitochondrially bound enzyme is more active than the soluble enzyme because the bound form can preferentially utilize ATP generated in the mitochondria and is less sensitive to G-6-P inhibition (104). G-6-P can inhibit hexokinase I activity either by a direct effect through allosteric inhibition (105) or by inducing the solubility of the

enzyme (106). Orthophosphate can reverse these inhibitory effects (106).

Hexokinase II is most abundantly expressed in insulin-responsive skeletal muscle and adipose tissues (107). Hexokinase II constitutes the vast majority of total hexokinase activity in muscle and plays an essential role in skeletal muscle glucose uptake (108). Under hyperglycemic-hyperinsulinemic clamp conditions, glucose transport and/or hexokinase activity was found to be diminished in persons with a strong family history of diabetes (77), whereas in transgenic animals with modestly increased levels of hexokinase II, glucose phosphorylation appeared rate limiting under similar conditions (108). Hexokinase II is largely cytosolic (109) but, like hexokinase I, may also be found bound to the mitochondria and can also be inhibited by G-6-P. Exercise (110), catecholamines (111), and insulin (107, 112) can all increase hexokinase II mRNA levels and activity and modify subcellular localization (112) in both skeletal muscle and adipose tissues. Multiple signaling pathways may be involved in the induction of hexokinase expression: in muscle, insulin utilizes the phosphatidylinositol 3-kinase (PI3K)/p70(s6k) dependent pathway (113), whereas in mesangial cells epidermal growth factor acts though the MAPK pathway (114). Homozygous hexokinase II-deficient mice die in the prenatal state, whereas heterozygotes lack any disturbances in glucose tolerance as assessed by glucose and insulin tolerance testing after either normal or provocative high-fat diets (115). Transgenic mice overexpressing hexokinase II demonstrate increased insulin and exercise-stimulated muscle glucose uptake *in vivo* (108, 116).

Hexokinase III is the principal isoform in the spleen and lymphocytes. The nuclear localization of the type III isozyme contrasts with the mitochondrial association of isoforms I and II (117). Hexokinase III appears to be expressed in cells involved in transport, secretion, and filtration functions and could play a role during development (103). However, little is known about the metabolic role of hexokinase III.

ii. Low-affinity hexokinases (type IV or glucokinase). Glucokinase (hexokinase IV) is predominantly expressed in liver and β-cells. Glucokinase exhibits a low affinity (between 6 and 11 mmol/liter) for glucose and is not inhibited by physiological concentrations of G-6-P. Glucokinase is the rate-limiting step for glucose metabolism in β-cells and is responsible for glucose-mediated regulation of insulin secretion (118). Expression of this enzyme is differentially regulated such that hepatic glucokinase is stimulated by insulin and inhibited by cAMP, whereas in β-cells its activity is increased by glucose (119, 120). In the β-cell, glucokinase activity is largely regulated by transcriptional mechanisms (17), whereas in liver, binding to glucokinase regulatory protein can also acutely regulate activity (121). In liver, glucokinase is sequestered in the nucleus with glucokinase regulatory protein at low concentrations of extracellular glucose (121).

The glucokinase gene has been characterized and is unusual as it contains two different transcriptional control domains. One region regulates transcription of the gene in the liver, whereas the other region, which lies at least 12 kb further upstream, controls transcription in the pancreatic β-cell. The finding of two different transcription control domains in a single glucokinase gene provides a genetic basis for the tissue-specific differential regulation of glucokinase. Interestingly, Leibiger *et al.* (19) showed that the insulin receptor isoform B, which is a splice variant of the receptor containing a 12-amino acid insert (exon 11) near the C terminus of the α-subunit, may preferentially regulate glucokinase gene expression in the β-cell compared with the insulin receptor isoform A, which does not contain the additional sequence. These findings suggest that insulin could increase glucokinase gene expression within the β-cell, a mechanism that could amplify the ability of the cells to sense glucose.

Transgenic animals with either liver or β-cell-specific knockouts help elucidate the complex role of glucokinase in each tissue. Whereas global or β-cell glucokinase-deficient mice die shortly after birth of severe diabetes, heterozygous animals survive but have moderate hyperglycemia. In contrast, mice without glucokinase in liver are only modestly hyperglycemic but have impaired glycogen synthesis and glucose turnover, as well as defects in insulin secretion in response to glucose (122).

b. Phosphatase: glucose-6-phosphatase. Glucose-6-phosphatase catalyzes the hydrolysis of G-6-P to produce glucose and phosphate. The enzyme is expressed mainly in the liver and kidney and is critical in providing glucose to other organs during prolonged fast or starvation. This enzyme is absent in muscle and other tissues, which therefore cannot release glucose to the bloodstream. Activity is inhibited by both insulin and glucose, which become elevated after feeding, thereby reducing endogenous glucose production in the fed state. Levels are increased by glucagon and glucocorticoids (123, 124). The enzyme is membrane-bound, associated with the endoplasmic reticulum. The enzyme glucose-6-phosphatase translocase acts to transport G-6-P from the cytoplasm to the lumen of the endoplasmic reticulum.

Deficiencies in glucose-6-phosphatase and glucose-6-phosphatase translocase cause glycogen storage disease type 1, characterized by growth retardation, hypoglycemia, hepatomegaly, kidney enlargement, hyperlipidemia, hyperuricemia, and lactic acidemia (125). Moreover, the overexpression of glucose-6-phosphatase in liver (126) or pancreas (127) induces insulin resistance in transgenic mouse models.

2. Implications of glucose phosphorylation for human type 2 diabetes

a. Hexokinase family

i. Hexokinase II. Hexokinase II levels have been found to be low in skeletal muscle of subjects with type 2 diabetes compared with matched controls (128). The decreased expression is muscle specific and is not seen in sc adipose tissue, implicating tissue specific alteration (129). Moreover, in healthy normal weight and obese persons evaluated after hyperinsulinemic clamp, hexokinase II gene expression is up-regulated in muscle and adipose tissues, whereas in type 2 diabetic subjects this up-regulation is blunted (129, 130). Although a polymorphic variant of hexokinase II has been identified, there is no apparent link between variants of this gene and type 2 diabetes (131, 132). Thus, it is unlikely that this polymorphism is the etiology of type 2 diabetes, and

regulation of protein expression or activity may be a consequence of diabetes *per se*.

ii. Glucokinase. A loss of function mutation of glucokinase was identified in some families with maturity onset diabetes of the young (MODY) (133–135). These patients demonstrate decreased glucose phosphorylation and decreased insulin secretion (17). The diabetes is often diagnosed in the second decade of life, is usually mild, and is often controlled by diet with or without a sulfonylurea drug (133). In one study, decreased liver glucokinase enzymatic activity was reported in type 2 diabetes (136), and functionally decreased glucose uptake and/or phosphorylation has been seen in several studies in humans *in vivo* (77, 137). Recently, these findings have been complemented by documented cases of hypoglycemia caused by an activating glucokinase mutation (138, 139). Although glucokinase regulatory protein has been postulated to be a candidate gene for type 2 diabetes, no mutations have been found to date in this gene in diabetic subjects (140), but its regulation is still under investigation. Although allosteric activators of glucokinase are under development (141), to date no drugs are yet available to specifically increase hexokinase activity, and the only current alternative to improve enzyme activity is to increase physical activity.

b. Phosphatase: glucose-6-phosphatase. In type 2 diabetic persons, the lack of suppression of hepatic glucose production in the setting of hyperglycemia and hyperinsulinemia is consistent with deficient inhibition of glucose-6-phosphatase activity or expression (142). Increased endogenous glucose production is a consistent feature of type 2 diabetes, and increased glucose-6-phosphatase activity has been demonstrated in type 2 diabetic subjects (143).

Metformin acts in part by decreasing endogenous glucose production (100). Although the mechanism of action of metformin is incompletely understood, it may involve the inhibition of glucose-6-phosphatase activity, with a glycogen-sparing effect (144). Some studies suggest that thiazolidinediones may share this property (145, 146). Because these drugs have different molecular mechanisms of action, these effects may be secondary to the altered metabolic environment or due to a convergence in their signaling pathways.

III. Glucose Utilization Pathways

There are three major pathways for the cellular fate of glucose, including: 1) oxidation to pyruvate, which may undergo further oxidation in the citric acid cycle; 2) storage as the polysaccharide glycogen for rapid utilization at a later time; and 3) conversion to other sugars and intermediates essential for other important biosynthetic and/or metabolic pathways (Fig. 2), which can include the generation of glycerol 3-phosphate used in triglyceride and phospholipid synthesis, a major cellular fate of glucose in adipose, muscle, and liver tissues. Glucose is an efficient fuel in that more ATP is produced per O_2 molecule when compared with oxidation of fat and other fuel sources. Moreover, glucose is unique in that its metabolism can furnish ATP even in the absence of oxygen.

A. Glucose phosphorylation and glycolysis pathways

1. Description of the pathways. A balance between hepatic gluconeogenesis and peripheral glycolysis is an important homeostatic function, especially during a prolonged fast. Glycolysis occurs with the oxidation of glucose to pyruvate and lactate and occurs in virtually all living cells. A continuous supply of glucose is necessary as a source of energy, especially for the nervous system whose cells have minimal storage capabilities and for erythrocytes, which are unable to store glucose or use other substrates as fuel.

a. Pyruvate formation. G-6-P is phosphorylated by phosphofructokinase to form fructose 1,6-diphosphate. The reaction is subject to allosteric control by cellular levels of ATP, AMP, and phosphate.

b. Krebs cycle/aerobic glycolysis. Under aerobic conditions, there can be complete oxidation of carbohydrates, fatty acids, and proteins to carbon dioxide and water, although glucose that enters the cycle can be released as lactate, pyruvate, and alanine particularly during conditions of a prolonged fast. Aerobic glycolysis yields the net production of 38 molecules of ATP per molecule of glucose consumed. Pyruvate crosses the mitochondrial membrane to supply fuel for the Krebs cycle (tricarboxylic acid cycle, citric acid cycle) or for gluconeogenesis. The pyruvate dehydrogenase complex determines the transformation of pyruvate to acetyl-CoA (coenzyme A). This enzyme complex is inactivated by ATP when cellular energy stores are high and by pyruvate dehydrogenase kinase (PDK) (147). PDK1-4 can regulate the pyruvate dehydrogenase complex by inhibitory phosphorylation of the complex. The enzymes PDK2 and PDK4 are expressed in most tissues, whereas PDK1 and PDK3 distribution is more limited. Levels of PDK4 are up-regulated during starvation, thereby inhibiting the complex when glucose conservation is necessary (148–150). Activity of the pyruvate dehydrogenase complex is a major determinant of the glucose oxidation rate. Glucose oxidation can then proceed though the Krebs cycle, a sequence of reactions in which acetyl-CoA is metabolized to CO_2 and hydrogen atoms. In brief, acetyl-CoA is first condensed with oxaloacetate to form citrate. In a series of seven subsequent reactions, two CO_2 molecules are split off, regenerating oxaloacetate (151). Exercise can increase the activity of pyruvate dehydrogenase (152), and pyruvate dehydrogenase activity is less responsive to insulin stimulation both in patients with diabetes and in their offspring (153). Because phosphorylated compounds are charged, most do not cross membranes, and pyruvate dehydrogenase activity remains within the mitochondria. Likewise, nicotinamide adenine dinucleotide (NADH) is not diffusible across membranes, so the reduction equivalents produced by Krebs cycle oxidation must be transferred to the cytoplasm by complex alternate reduction-reoxidation cycles involving a membrane diffusible substrate such as malate. The inner mitochondrial membrane contains the respiratory chain proteins, which consist of a series of electron acceptors that are reversibly reduced and then reoxidized as they receive electrons and form ATP. Mitochondria are often located near subcellular structures that require energy or provide a substrate source (154). Moreover, mitochondrial processes are

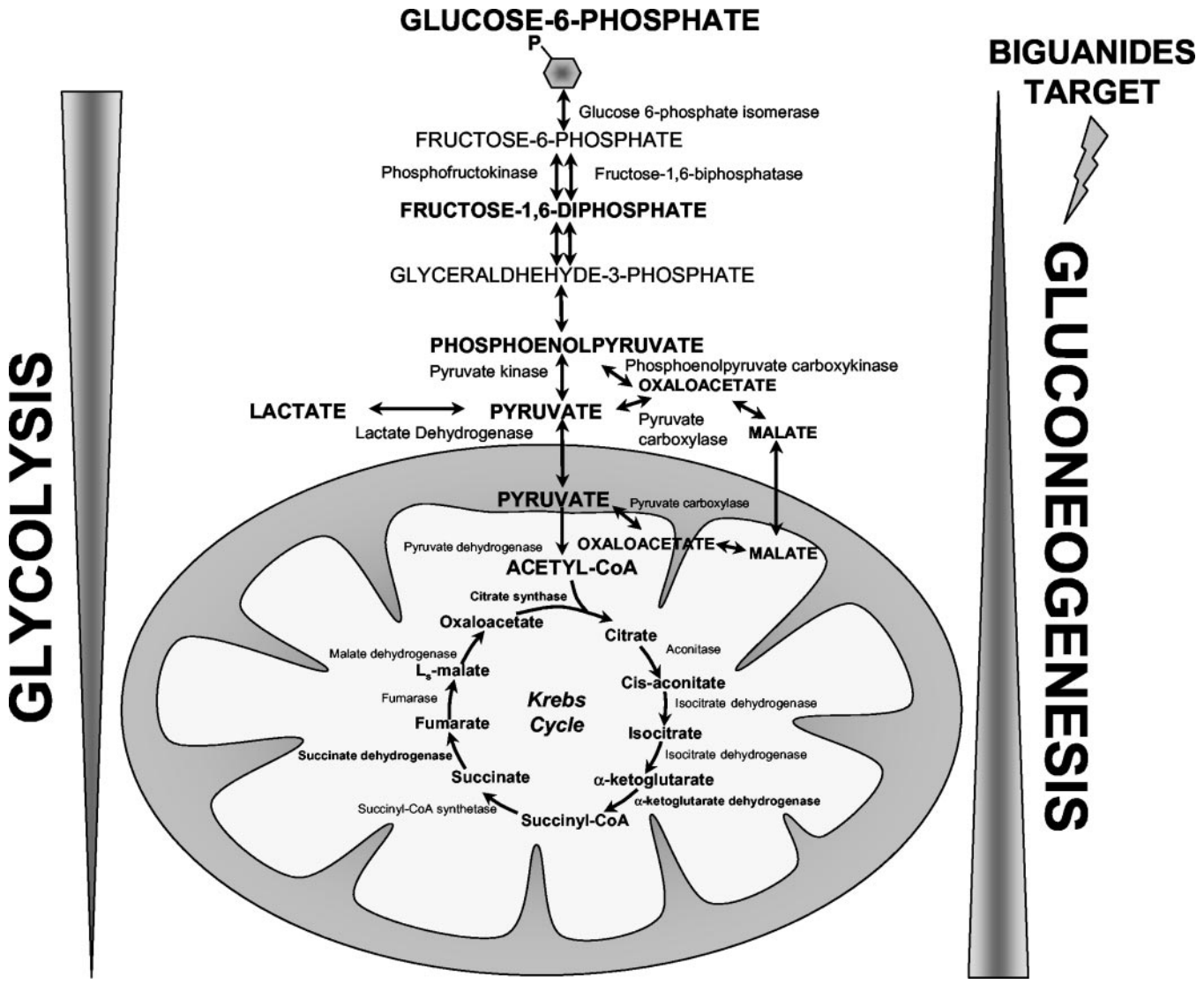

FIG. 2. Aerobic and anaerobic glycolysis and gluconeogenesis pathways are illustrated.

coupled to peripheral glucose uptake, phosphorylation, and glycolysis by the spatial proximity to hexokinases (reviewed in Ref. 155).

The Randle cycle provides an important link between glucose and fatty acid metabolism (156) whereby fatty acid or ketone oxidation leads to elevation of mitochondrial acetyl-CoA and NADH, leading to increases in cytosolic citrate. Increased cytosolic citrate could inhibit glycolysis at the level of phosphofructokinase, thereby decreasing the use of glucose as a fuel while increasing glucose incorporation into glycogen (157, 158). Malonyl-CoA, which is involved in the regulation of the transfer of long-chain fatty acids into the mitochondria has been proposed to play a central role in this process mediating fuel sensing, glucose metabolism, and insulin action (159, 160).

Mitochondria and glycolytic processes are also coupled with insulin secretion. As a result of glycolysis, rising ATP levels lead to the closure of ATP-dependent potassium channels and opening of calcium channels, which triggers insulin secretion. The role of mitochondria in insulin secretion is highlighted by the finding of defective insulin secretion followed by β-cell loss in transgenic rodents with pancreatic β-cell-specific disruption of mitochondrial transcription factor A (161).

Krebs cycle activity is not regulated solely by the mitochondrial acetyl-CoA concentration. Pathway activity varies over a wide range depending on the substrate source; for example, acetyl-CoA levels may be 10-fold lower with glucose compared with fatty acid as a substrate source for the same cycle flux (162). Citrate synthase, isocitrate, and α-ketoglutarate dehydrogenases are generally considered to be important regulatory enzymes controlling flux through the entire Krebs cycle (163). The pyridine nucleotide redox potential (NADH/NAD+ ratio), the matrix phosphorylation potential (P_I+ADP/ATP ratio), and the Ca^{2+} concentration act as key regulatory factors at several steps of the cycle (163). Krebs cycle activity is further influenced by thyroid hormone, adrenergic compounds, and glucocorticoids (162, 163).

Few cases with primary disorders of enzymes of the Krebs

cycle have been reported in humans. However, increased PDK4 activity can be seen in insulin resistance and type 2 diabetes, may be a direct or indirect target of PPARα, and could represent an additional drug target for these medical conditions (164, 165). Deficiency of α-ketoglutarate dehydrogenase, succinate dehydrogenase, and fumarase has been reported in rare patients and leads to neurological impairment with or without muscular involvement (163). Germline mutations of succinate dehydrogenase cause hereditary paraganglioma and pheochromocytoma (166). More recently, mutations of fumarate hydratase have been associated with uterine fibroids, skin leiomata, and, to a lesser extent, papillary renal cell cancer (167). Because neural cells are most dependent on glucose oxidation for fuel, it is not surprising that disorders of these key enzymes are clinically manifest in these tissues, without abnormalities in blood glucose or insulin levels.

c. Anaerobic glycolysis: the Embden-Meyerhof-Parnas pathway. In erythrocytes, the glycolytic pathway always terminates in the formation of lactate, because these cells lack enzymes of the Krebs cycle. However, in other tissues under anaerobic conditions, glucose is used to generate high-energy ATP as fuel, with formation of lactate as a byproduct. The reaction is catalyzed by lactate dehydrogenase, and in contrast to the Krebs cycle, which occurs in both cytosolic and mitochondrial compartments, all the enzymes of the Embden-Meyerhof-Parnas pathway are found in the cytosol. Under anaerobic conditions, glucose is the only fuel source that can be used by skeletal muscle, and during muscle contraction a continuous supply of ATP is necessary. Anaerobic glycolysis yields the net production of only two molecules of ATP and only two molecules of reduced NADH per molecule of glucose consumed. Thus, anaerobic metabolism is inefficient and cannot be sustained for long intervals of time. In addition to erythrocytes and skeletal muscle, other tissues that produce lactate include brain, gastrointestinal tract, renal medulla, adipose tissue, and skin. Lactate can be converted back into glucose by the gluconeogenesis pathway, requiring ATP (168), or can be used in muscle to help restore glycogen after intense exercise (169). The energy potential of lactic acid can only be recovered in the presence of oxygen with conversion back to pyruvic acid. In turn, pyruvate can then be metabolized in the citric acid cycle.

d. Gluconeogenesis. Gluconeogenesis provides glucose to the tissues of the body in the fasted state when dietary carbohydrates are not available, by formation of glucose or glycogen from noncarbohydrate sources. In addition, the gluconeogenic process clears metabolic products, such as lactate produced by muscle and erythrocytes and glycerol produced by adipose tissue, from the circulation. The regulation of endogenous glucose production is central to the control of blood glucose concentrations, and the liver and kidney are the principal organs responsible for gluconeogenesis.

Many of the enzymes of glycolysis and gluconeogenesis are shared, including those from phosphoenolpyruvate to fructose 1,6-diphosphate. In liver, glucose-6-phosphatase catalyzes the rate-limiting step of gluconeogenesis. However, for gluconeogenesis to occur, the enzymes pyruvate carboxylase and phosphoenol pyruvate carboxylase must be present and can limit flux through the gluconeogenic pathway (reviewed in Ref. 170).

2. Implications of altered glycolysis and gluconeogenesis in type 2 diabetes

a. Formation of pyruvate and aerobic glycolysis. The rate of glucose oxidation depends on glucose flux, which reflects circulating levels of both glucose and insulin. In persons with type 2 diabetes studied under euglycemic and moderately hyperinsulinemic conditions, glucose oxidation is significantly impaired when compared with nondiabetic subjects (171). However, some studies performed under hyperglycemic conditions demonstrate that a mass action effect of glucose can partially compensate for the marked decrease in insulin-stimulated glucose uptake, allowing for preservation of glucose oxidation in persons with diabetes (172, 173). However, other studies do not confirm these results (171), perhaps due to different levels of glucose or insulin achieved.

β-cell glycolysis increases insulin secretion in a glucose concentration-dependent manner and could provide a link between impaired glucose metabolism and impaired insulin secretion (174). Indeed, diminished glycolysis has been directly implicated in specific cases of type 2 diabetes. Deficiency in phosphofructokinase activity due to a heterozygous gene mutation has been reported in one Ashkenazi-Jewish type 2 diabetic family (175). Increased PDK activity, which would act to decrease activity of pyruvate kinase, has been demonstrated in the setting of insulin resistance and type 2 diabetes in obese and Pima Indian subjects (176, 177) and could be involved in the pathogenesis of the disease or represent a molecular target for therapeutic intervention (149).

Many of the steps of the aerobic glycolysis process occur in the mitochondria. Thus, mitochondrial alterations could play an important role in the cellular fate of glucose and the pathogenesis of diabetes. Indeed, mitochondria have been demonstrated to play an important role in the pathogenesis of several specific forms of diabetes including Wolfram's syndrome (DIDMOAD), Freidreich's ataxia, and HIV lipodystrophy. Their function is intimately related to both insulin action and secretion (178, 179). Mutations in mitochondrial DNA have been suggested to account for up to 1% of diabetes (180). Diminished mitochondrial content in circulating cells is associated with decreased insulin sensitivity (181) and could be a marker of altered content in insulin-responsive tissues. More specifically, mitochondrial area and function are decreased in muscle of obese and diabetic persons (182), and mitochondrial activity correlates closely to measures of insulin sensitivity. Likewise, mitochondrial dysfunction and decreased flux through the tricarboxylic acid cycle have been demonstrated to play an important role in the insulin resistance of aging (183). New molecular approaches using gene expression profiling with high-density oligonucleotide arrays have demonstrated reductions in the genes encoding many of the key enzymes involved in glycolysis, oxidative metabolism, and mitochondrial function associated with progressive insulin resistance and diabetes (184–186) in diverse populations including the Pima Indians, Mexican-

American, and European Caucasians. Transcription factors that coordinately regulate genes encoding mitochondrial function likely effect the altered expression of the genes regulating oxidative phosphorylation. PGC-1α is one such coactivator, discovered and named for its role in modulating PPARγ activity (187), and levels are altered both in patients with diabetes and in offspring of diabetic parents who are at high risk for developing the disease (185, 186).

PGC-1α is a major coactivator of nuclear encoded mitochondrial genes. Overexpression of PGC-1α increases mitochondrial biosynthesis, nuclear and mitochondrial gene expression, and muscle oxidative fiber types (reviewed in Ref. 188). PGC-1α maps to chromosome 4p15, a locus associated with obesity (189). Polymorphisms in the PGC-1α gene have been associated with diabetes in Danish Caucasians (190), although this has not been replicated in French populations (191). Of interest, recent studies show decreased levels of PGC-1α in muscle of persons with diabetes or a family history of diabetes, and levels correlate with insulin-mediated glucose disposal (185, 186).

In addition, hyperglycemia-induced overproduction of superoxide by the mitochondrial electron transport chain may play a central role in mediating multiple mechanisms of hyperglycemic complications of diabetes via inhibition of the glycolytic protein glyceraldehyde-3-phosphate dehydrogenase (GAPDH). In addition to its role in glycolysis, GAPDH has many cellular functions. As a membrane protein, GAPDH is involved in endocytosis; in the cytoplasm, it participates in control of gene expression; and in the nucleus, it is involved in DNA replication and repair, as well as tRNA export (192). Recent work suggests that inhibition of GAPDH could functionally divert upstream glycolytic metabolites into three major pathways mediating hyperglycemic damage, including activation of protein kinase C (PKC) isoforms, hexosamine pathway flux, and advanced glycation end product formation (193). In theory, pharmacological protection of GAPDH activity would have a protective role in prevention of diabetic complications.

b. Gluconeogenesis. A gradual and progressive increase in endogenous glucose production contributes to hyperglycemia in persons with type 2 diabetes. In the fasted state, gluconeogenesis is increased in diabetic compared with control persons and is incompletely suppressed by insulin in the postprandial state (194). Thus, increased hepatic glucose production contributes to hyperglycemia in both the fasting and postprandial states. Although the basis of increased gluconeogenesis is not known, it is not due to genetic mutation or polymorphism of the glucose-6-phosphatase gene or promoter (195). Recent studies suggest an important role for elevated free fatty acids, as may be seen in visceral obesity, in the increased output of glucose from the liver (196, 197).

Metformin, commonly prescribed for the treatment of diabetes and other insulin-resistant conditions, reduces hepatic glucose production. In addition to the effects on glycogenolysis previously discussed, it may also reduce gluconeogenesis, demonstrating the therapeutic benefit of manipulation of this pathway (198, 199). The exact mechanism is still unclear, and various mechanisms have been proposed, including modification of lactate uptake (200) or pyruvate kinase activity (201) and decreased flux through pyruvate carboxylase-phosphoenolpyruvate carboxykinase (202). Multiple studies support a direct role in activation of AMPK, a major regulator of both glucose and lipid metabolism in both liver and skeletal muscle (94, 203). Thiazolidinediones suppress hepatic gluconeogenesis *in vitro* and *in vivo* in animal models (204), with a decrease in lactate-stimulated gluconeogenesis and elevations in fructose 2,6-biphosphate concentrations (205), via decreased expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (146). However, thiazolidinediones appear to have more modest effects on hepatic glucose production in type 2 diabetic humans (100).

Although sulfonylureas exert their principal hypoglycemic effect through stimulation of insulin secretion, some studies suggest that they are able to suppress endogenous glucose production, acutely and chronically, by a potentiation of insulin action (206–208). Although these effects could be mediated by improvements in glucotoxicity, animal data support a direct effect via inhibition of lactate gluconeogenesis (209).

c. Anaerobic glycolysis: the Embden-Meyerhof-Parnas pathway. Elevated plasma lactate levels have been demonstrated to be an independent risk factor for the development of type 2 diabetes in prospective epidemiological studies (210). In normoglycemic first-degree relatives of type 2 diabetic subjects, elevated lactate levels are generated by increased release from adipose tissue (211). In type 2 diabetic patients, lactate and pyruvate interconversion rates are greatly enhanced, possibly due to concomitant impairment in the glucose oxidative pathway (212). This hyperlactinemia may lead to insulin resistance by increased gluconeogenesis in liver and decreased glucose uptake in muscle (213). Although animal studies support this hypothesis (214), human studies evaluating the effect of lactate infusion do not support an insulin-resistant effect (215–217). However, an alternate mechanism to explain the correlation between increased hepatic gluconeogenesis and decreased glucose use by muscle seen when plasma lactate levels are elevated could be the effect of alterations in fatty acid oxidation, with increased gluconeogenesis from lactate (218, 219) and concomitant inhibition of pyruvate dehydrogenase activity in muscle (220).

B. Glycogen synthesis and breakdown pathways

Glycogen, the primary storage form for glucose in mammalian cells, is critical to glucose homeostasis (Fig. 3).

1. Description of the pathway

a. Glycogen synthesis. Although many cells are capable of synthesizing glycogen for storage for future needs, glucose is converted into glycogen primarily in muscle, where it provides energy for contraction, and in liver, from which it can be exported to maintain constant blood glucose levels.

Mammalian glycogen is a branching treelike structure, and biosynthesis involves two stages. The first step involves the formation of glycoprotein by self-glucosylation of glycogenin to form a covalently linked oligosaccharide. The second step is elongation involving the bulk synthesis of glycogen through the reaction catalyzed by glycogen syn-

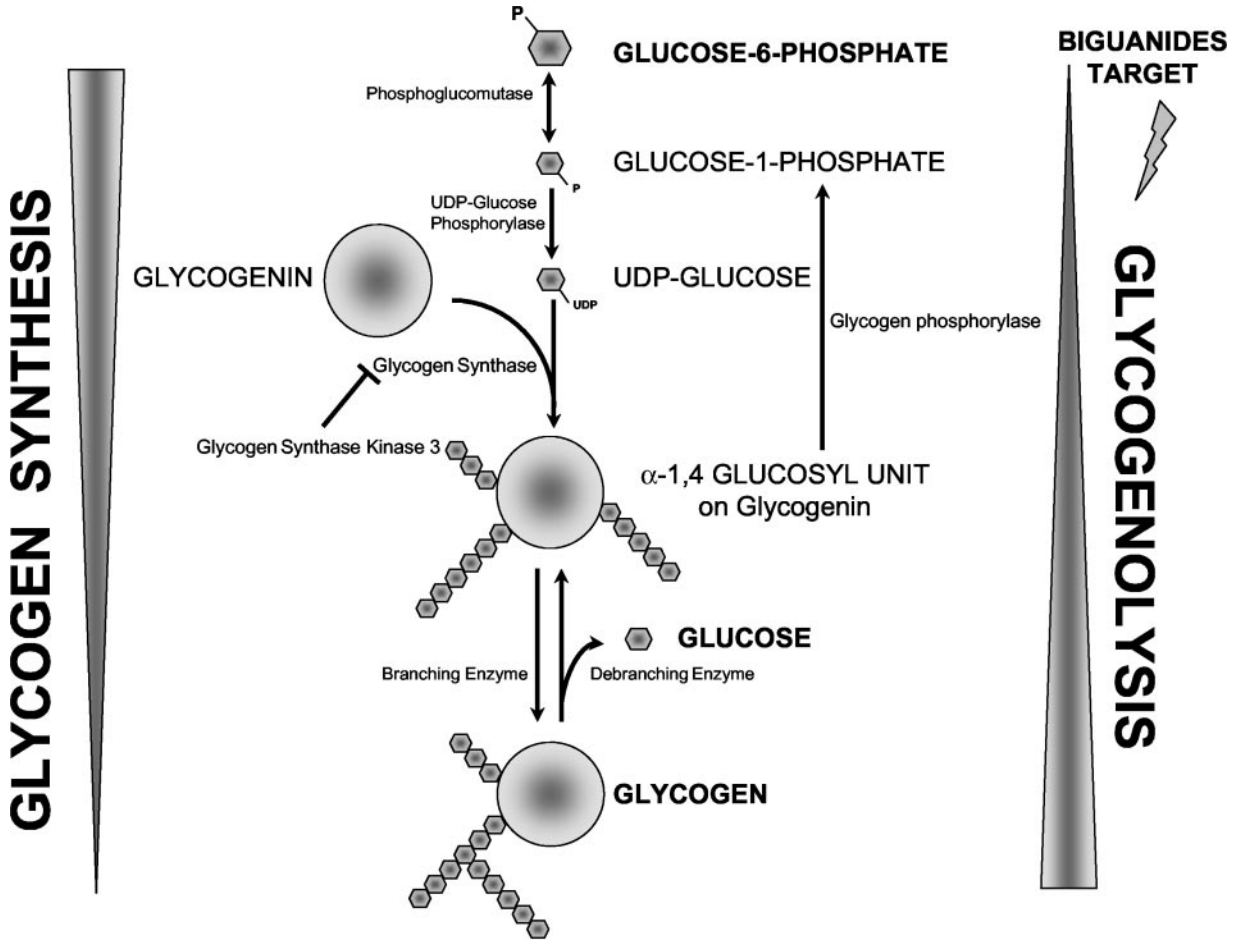

FIG. 3. Glycogen synthesis and glycogen breakdown.

thase and branching enzyme (Fig. 3). Glycogen synthesis releases pyrophosphate, which is immediately hydrolyzed by pyrophosphatases, assuring the unidirectionality of the reaction. The enzymes catalyzing the synthesis of glycogen are separate from those catalyzing glycogenolysis, and both are under control of phosphorylation-dephosphorylation cycles. The phosphorylations are catalyzed by protein kinases subject to cAMP regulation and consequently are subject to hormonal control.

The storage polysaccharide glycogen is intimately linked with insulin action and blood glucose homeostasis. Skeletal muscle is the major site of insulin-simulated glucose uptake, and most of the glucose that enters human muscle fibers in response to insulin is deposited as glycogen (221, 222).

i. Phosphoglucomutase and uridine diphosphate (UDP)-glucose pyrophosphorylase. After glucose enters cells, it is phosphorylated by hexokinase to form G-6-P, as previously discussed (*Section II.B*). Phosphoglucomutase promotes the isomerization of G-6-P to glucose-1-phosphate. Glucose-1-phosphate is then converted to uridine diphosphoglucose by UDP-glucose pyrophosphorylase. There are four distinct isoforms of phosphoglucomutase, which occur in varying proportions in different tissues. In women, genetic polymorphisms of phosphoglucomutase are associated with recurrent spontaneous abortion (223).

ii. Glycogen synthase. Glycogen synthase is the rate-limiting enzyme in glycogen synthesis, and its activity is modulated by phosphorylation/dephosphorylation, such that phosphorylation generally decreases activity. Glycogen synthase is phosphorylated at nine or more sites by protein kinases, including cAMP-dependent protein kinase A (PKA), calmodulin-dependent kinases, glycogen synthase kinase 3 (GSK-3), PKC, and others. In addition to the phosphorylation state, the activity of glycogen synthase also depends on allosteric regulation by substrates, principally G-6-P (224). UDP-glucose serves as the glycosyl donor for the initial step of glycogen formation, mediated by the initiator protein glycogenin, and for the subsequent steps mediated by glycogen synthase and the branching enzyme (224–226). UDP-glucose is the scaffolding protein of glycogen synthesis. In mice, glucose transport and hexokinases are not the rate-limiting steps for glycogen synthesis as shown by constitutively active glycogen synthase transgenic models (227). Mutations in glycogen synthase are responsible for glycogen storage disease type 0 in humans, which is characterized by hypoglycemia in infancy (228).

Two different mechanisms exist to stimulate glycogen synthesis: one in response to insulin, and the other acting in response to glucose after glycogen depletion (229). The molecular mechanism by which insulin activates glycogen syn-

thase remains controversial (230). Insulin is thought to activate glycogen synthase by causing its dephosphorylation, involving the phosphatases protein phosphatase-1 (PP1) and the glycogen-bound form of PP1. Initially, insulin was thought to stimulate phosphatase activity by phosphorylation of the MAPK pathway, but further evidence suggests that insulin may act via the protein kinase B (also known as AKT) pathway, resulting in the inactivation of GSK-3. Furthermore, glycogen synthase exhibits important spatial organization. In muscle and liver, glycogen synthase is translocated from an intracellular site to the membrane in response to glucose and insulin (231, 232).

iii. PP1. The insulin-dependent dephosphorylation of glycogen synthase is catalyzed by PP1 (233, 234). PP1 also catalyzes the dephosphorylation and inactivation of glycogen phosphorylase, which contributes to increased glycogen deposition. PP1 interacts with a wide variety of protein regulatory subunits and targets glycogen via several glycogen-targeting subunits (235). PP1R3A is the most abundant glycogen-targeting subunit in rodent skeletal muscle, and disruption of this gene in mice leads to obesity and glucose intolerance (236).

iv. GSK-3. The enzyme GSK-3 is a highly regulated multifunctional serine/threonine kinase that phosphorylates glycogen synthase and PP1, permitting increased glycogen formation. Activity of GSK-3 can be regulated through three distinct signaling mechanisms (Fig. 4), with phosphorylation of GSK-3 resulting in inhibition of its protein kinase activity. Insulin, IGF-I, and platelet-derived growth factor all inhibit GSK-3 via the phosphatidylinositol-3-kinase (PI3K)/protein kinase B pathway (225, 237). Changes in intracellular levels of cAMP regulate GSK-3 activity by cAMP-dependent PKA phosphorylation; and PKC proteins (α, β, γ, η, δ) phosphorylate GSK-3 by activation of PKCβ by lysophosphatidic acid (238).

Initially identified as a regulator of glycogen synthesis, GSK-3 also plays an important physiological role in coupling metabolism and protein synthesis in response to growth factor stimulation. GSK-3 regulates several signal transduction pathways including PI3K (239), Wnt/wingless (240), and nuclear factor-κB (241), which influence survival, proliferation, and inflammatory processes, respectively.

v. Glycogen branching enzyme. The final step in glycogen biosynthesis is catalyzed by glycogen branching enzyme transferase that attaches short glycosyl chains in α-1,6-glucosidic bonds to peripheral chains of nascent glycogen. Branching enzyme deficiency (glycogen storage disease type IV) is characterized by progressive liver cirrhosis occurring in childhood (242).

vi. Glycogenin. Glycogenin is itself an enzyme that catalyzes the transfer of glucose residues from UDP-glucose in a self-glucosylation process that involves the modification of one subunit by the other. The protein glycogenin is a specialized initiator protein, up to about 10 residues long, which serves as a substrate for elongation by glycogen synthase and the branching enzyme and leads to the formation of an oligosaccharide chain. Humans express two forms of glycogenin. Type 1 is widely expressed, whereas type 2 is predominantly expressed in liver, but also in the heart and pancreas. Overexpression of glycogenin-2 in rat fibroblast cells results in increased glycogen accumulation (243). Glycogenin function can be regulated through protein–protein interactions including autodimerization (244), complex formation with glycogen synthase (245), colocalization with actin (246), and activation by glycogenin-interacting protein (247).

b. Glycogen breakdown or glycogenolysis. Complete glycogen breakdown provides glucose during fasting or exercise and requires the concomitant action of both glycogen phosphorylase and glycogen debranching enzyme. In contrast to liver, which can export hexoses for the maintenance of blood glucose, muscle glycogen provides fuel for glycolysis only within muscle tissue itself.

i. Glycogen phosphorylase. There are three isoforms of glycogen phosphorylase encoded by three different genes, each with different expression levels in muscle, liver, and brain. Glycogen phosphorylase catalyzes the degradation of glycogen by phosphorolytic cleavage of α-1,4-glycosidic bonds to form glucose-1-phosphate. Activity is regulated by allosteric ligands, such as AMP and G-6-P, and by phosphory-

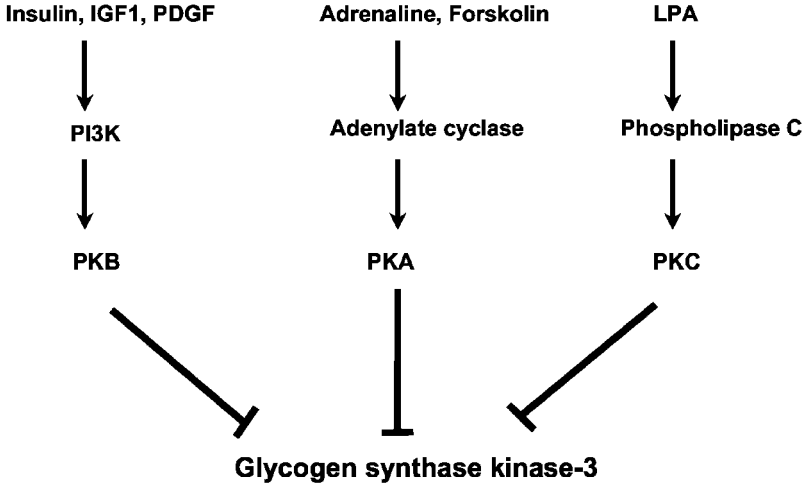

FIG. 4. Mechanisms of GSK-3 inhibition.

lation (248). Glycogen phosphorylase is activated by phosphorylation by phosphorylase kinase, which is controlled by neural and hormonal signals. In turn, phosphorylase kinase is activated by phosphorylation by cAMP-dependent protein kinase. Glucagon is the principal activator in liver, whereas in muscle it is adrenaline. Both hormones activate the membrane protein adenylate cyclase through their respective receptors. The liberation of cAMP allows the activation of cAMP-dependent protein kinase, resulting in glycogen phosphorylase activation (249). Deficiency of glycogen phosphorylase in liver is responsible for glycogen storage disease type VI, characterized by hepatomegaly and growth retardation (250). Muscle glycogen phosphorylase deficiency leads to glycogen storage disease type V, characterized by exercise intolerance (251).

ii. Glycogen debranching enzyme. The debranching enzyme possesses two catalytic activities, hydrolyzing the α-1,6 bond during glycogen degradation and providing a small amount of free glucose. Genetic defects of this enzyme cause glycogen storage disease type III, characterized by hypoglycemia, hepatomegaly, short stature, and myopathy (252).

2. Role of impaired glycogen synthesis and breakdown in human type 2 diabetes. Insulin resistance is a major feature of type 2 diabetes and *in vivo* can be attributed largely to defects in muscle glycogen storage.

a. Glycogen synthesis. In type 2 diabetic patients, *in vivo* measurements of insulin resistance are largely attributed to diminished glucose uptake in skeletal muscle and liver secondary to reduced insulin stimulated glucose transport, hexokinase activity, and glycogen synthesis. Nuclear magnetic resonance studies, performed during hyperglycemic-hyperinsulinemic clamps, suggest that impaired insulin-stimulated glucose transport may underlie the decreased insulin-stimulated muscle glycogen synthesis in type 2 diabetics (76). Although glycogen synthase activity is impaired in type 2 diabetes, it remains uncertain whether these defects are primary or a consequence of hyperglycemia *per se*. Despite a reduced activity in muscle of type 2 diabetes, glycogen synthase expression is normal, suggesting altered regulation. Normalization of plasma glucose concentration in type 2 diabetic patients by diet or insulin therapy improves insulin-stimulated glycogen synthesis, suggesting that these abnormalities may be secondary to hyperglycemia *per se* (253, 254). In an interesting study of monozygotic twin pairs discordant for type 2 diabetes, insulin stimulation of glycogen synthase expression was only impaired in muscle of the affected twin (255). However, other studies suggest an impaired activation of glycogen synthase in people at risk for developing type 2 diabetes, suggesting a primary defect in the pathogenesis of the disease (256–258). One study reports an association between polymorphisms of the glycogen synthase gene and a subgroup of type 2 diabetic subjects characterized by hypertension and marked insulin resistance (259). However, studies using mutational analysis of the glycogen synthase gene do not provide evidence for a primary role in insulin resistance or diabetes (260, 261). Furthermore, hyperglycemia in the absence of hyperinsulinemia obtained by hyperglycemic-euinsulinemic clamp studies is capable of completely normalizing glycogen synthesis in type 2 diabetic subjects (142, 173).

Despite the controversial primary or secondary role of glycogen synthase in diabetes, the glycogenolysis pathway remains under investigation for its role in diabetes pathogenesis and as a potential molecular target for novel pharmacological therapies. Metformin inhibits hepatic glucose production, although the relative importance of its effects on glycogenolysis (262) or suppression of gluconeogenesis (198) remains controversial. Differences between studies may be explained in part by the activity of the target enzyme AMPK activity in response to differing cellular substrate availability between the different studies (203, 263). Although sulfonylureas can activate glycogen phosphorylase and mobilize glycogen stores through a calcium-dependent mechanism in hepatocytes *in vitro* (209, 264), this action has never been demonstrated *in vivo*.

GSK-3 protein levels and activity are elevated in muscle of type 2 diabetic patients, and levels are inversely correlated with both glycogen synthase activity and muscular insulin resistance (265). However, no structural changes have been detected in analysis of the coding region of the two isoforms of GSK-3 (266). Inhibition of GSK-3 improves insulin action and glucose metabolism when assessed in human skeletal muscle *in vitro*, and in rodents *in vivo*, representing a promising target under development for future therapeutic intervention in type 2 diabetes (267–269).

Of interest, mutations or polymorphisms of the glycogen-associated regulatory subunit of PP1, PP1R3, have been associated with insulin resistance in animal models and some, but not all, human studies (270–276). These findings implicate PP1 as a potential therapeutic target for drug development.

b. Glycogen breakdown. The lack of suppression of glycogen synthase by glucagon in the liver may contribute to postprandial hyperglycemia in type 2 diabetes by maintaining glycogen phosphorylase in an activated state resulting in persistent glycogenolysis (277). Reductions in fasting blood sugar during energy restriction in type 2 diabetic patients are largely due to decreased glycogenolysis with little change in absolute gluconeogenesis (278). Thus, glycogen phosphorylase or glycogenolysis inhibitors could prove useful in the treatment of type 2 diabetes (279). The potential role of glycogen phosphorylase inhibition as a therapeutic target is further supported by the closely coupled enzymatic activity of glycogen synthase and phosphorylase such that low levels of phosphorylase expression can inhibit synthase activity, and likewise phosphorylase inhibitors can enhance synthase activity in hepatocytes (280).

C. Pentose phosphatase shunt/hexose monophosphate pathway

The pentose phosphate shunt is an alternative pathway for glucose metabolism that generates NADPH (Fig. 5) and is useful in maintaining the integrity of red blood cell membranes, in lipid and steroid biosynthesis, and in hydroxylation and anabolic reactions. This pathway is notably active in liver, lactating mammary glands, and adipose tissue.

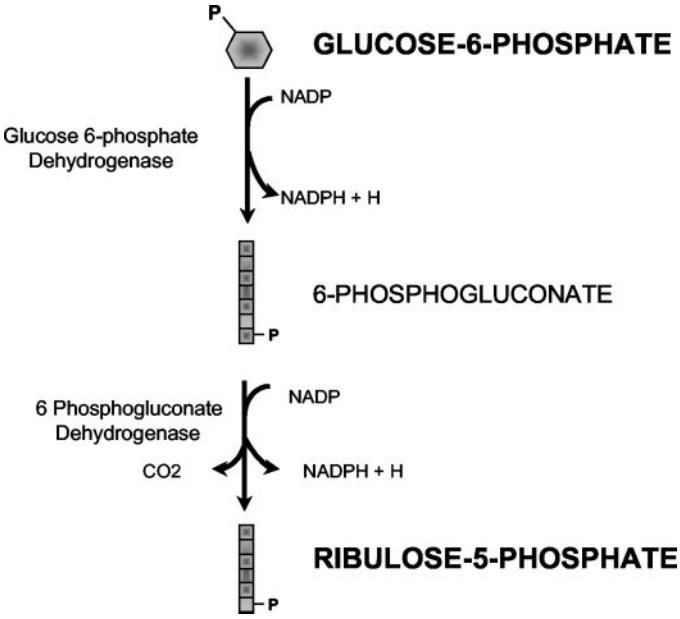

FIG. 5. Review of pentose phosphate shunt.

The percentage of glucose catabolized through the hexose monophosphate pathway varies between tissues, and this fraction can be increased during oxidative stress. With increased oxidative stress in diabetes, it is likely that this pathway is more active in the disease state, although the pathway has not been shown to participate directly in the pathogenesis of the disorder (281).

G-6-P dehydrogenase deficiency is responsible for a type of X-linked hemolytic anemia, which is more common among persons of Mediterranean descent (282).

D. Hexosamine biosynthesis pathway

With the exception of the first step in the hexosamine biosynthetic pathway, the enzymatic reactions are irreversible and do not require ATP or the participation of any cofactors (Fig. 6).

1. G-6-P isomerase. G-6-P isomerase is a dimeric enzyme that catalyzes the reversible interconversion of G-6-P and fructose-6-phosphate (fructose-6-P). G-6-P isomerase deficiency is responsible for nonspherocytic hemolytic anemia of variable severity associated in some cases with neurological impairment (283).

2. Glutamine fructose-6-P amidotransferase. The glucosamine pathway diverts 2–3% of the fructose-6-P derived from glucose into glucosamine-6-phosphate, thus giving rise to obligatory substrates for the synthesis of glycoproteins and glycolipids (284).

Glutamine fructose-6-P amidotransferase (also called synthase) is the first and rate-limiting enzyme in hexosamine biosynthesis and catalyzes an essentially irreversible reaction. This enzyme exhibits absolute specificity for L-glutamine as an amino donor and for D-fructose-6-P as an acceptor substrate to produce one molecule of glutamate and one molecule of aminated product. Several independent reports demonstrate that tissue enzyme activity levels may be mediated by sex hormones, resulting in increased activity with testosterone and estradiol, and antagonism by progesterone and GnRH (285). The enzyme is subject to feedback inhibition by UDP-*N*-acetylglucosamine and can be experimentally inhibited by glutamine analogs.

The final step in the hexosamine biosynthesis pathway is the formation of UDP-*N*-acetylglucosamine and other nucleotide hexosamines, which are major substrates for glycosylation of proteins. Many cytoplasmic and nuclear proteins are glycosylated on their serine and/or threonine residues by the addition of a single molecule of O-linked β-*N*-acetylglucosamine (286). In particular, several transcription factors undergo this type of rapid modification, causing alterations in their activity and/or stability. Thereby the hexosamine pathway can mediate the effects of glucose on the expression of several gene products and thereby participate in glucotoxicity or glucose-induced insulin resistance (284, 287, 288), and it is linked to glucose-induced changes in cell growth.

The hexosamine pathway is a cellular sensor of energy availability. It is able to modify the expression of a cluster of nuclear-encoded mitochondrial genes involved in oxidative phosphorylation in muscle and fat and the expression of leptin in adipocytes (289, 290). Activation of the hexosamine biosynthesis pathway via these transcriptional changes markedly decreases whole-body energy expenditure (290).

In vivo, in rodents, increasing the amount of flux into the hexosamine pathway by various means has been shown to induce defects involved in insulin secretion and action, including diminished insulin-stimulated glucose uptake (291), GLUT4 translocation (292, 293), glycogen synthase activity and glycogen synthesis (293–295), hepatic glucokinase activity and endogenous glucose production (296), β-cell glucokinase activity and insulin secretion (297), and pyruvate kinase (298) and PI3K activity (299). Effectively, when rodents are infused with glucosamine, there is reduced glucose uptake as assessed by euglycemic-hyperinsulinemic clamp (291).

Sequelae of hexosamine pathway activation are common features involved in insulin resistance and the pathogenesis of type 2 diabetes. Transgenic mouse models that overexpress glutamine fructose-6-P amidotransferase (GFAT) in skeletal muscle and fat demonstrate insulin resistance (300). Furthermore, overexpression of GFAT in pancreatic β-cells of transgenic mice leads to hyperinsulinemia, insulin resistance, obesity, and the development of mild type 2 diabetes in males (301).

3. Implications for type 2 diabetes in humans. The hexosamine biosynthesis pathway may be the mechanism by which cells sense ambient glucose levels, and when glucose flux is excessive, respond by down-regulating glucose transport, leading to insulin resistance (284). GFAT levels are markedly elevated in skeletal muscle of human type 2 patients, and chronic hyperglycemia is also associated with increased enzyme activity (302). GFAT activity from muscle biopsy studies is negatively correlated with measured glucose uptake during euglycemic-hyperinsulinemic clamp studies and

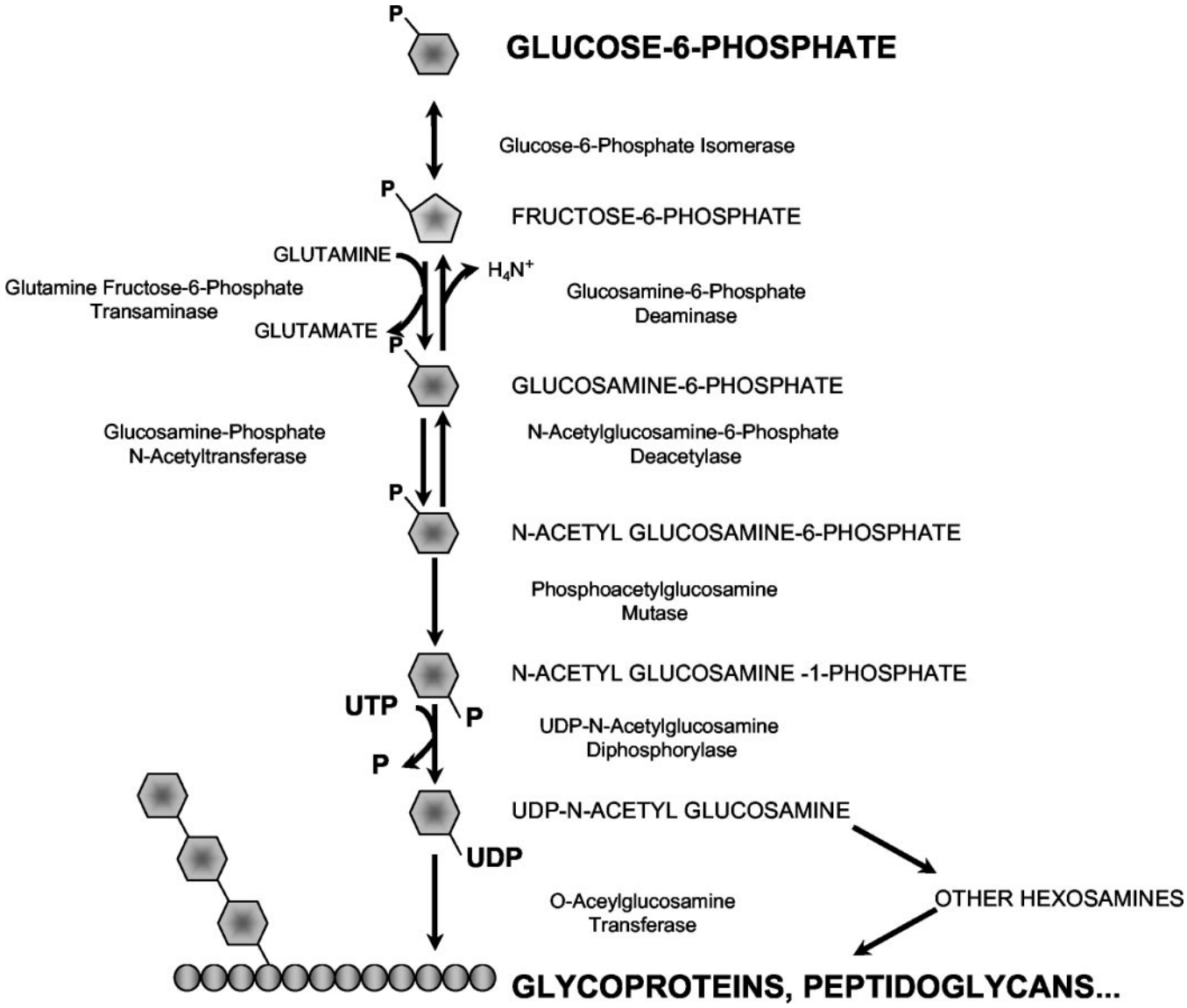

FIG. 6. Hexosamine biosynthesis pathway.

has also been shown to correlate with obesity. However, differences in activity between diabetic and control subjects disappear after culturing skeletal muscle cells from these subjects under conditions of controlled glucose and insulin concentrations, suggesting that the defects are acquired and not primary (303). Consistent with data from muscle, there is a good correlation between GFAT activity, body weight, and leptin levels in human adipose tissue obtained by biopsy (304). Moreover, in human cultured adipocytes, inhibition of glucosamine production reduced glucose-stimulated leptin release and ob-gene expression, implying that hexosamine biosynthesis regulates leptin production in human adipose tissue (304).

In studies of healthy humans, acute glucosamine infusion appears to mimic many metabolic features of human diabetes. High levels of glucosamine decreased insulin sensitivity (assessed as the insulin sensitivity index) and S_G during iv glucose tolerance testing, resulting in a mild β-cell impairment. However, no effect on insulin sensitivity was demonstrated when assessed under euglycemic hyperinsulinemic conditions (305).

The hexosamine pathway appears to mediate many of the adverse effects of glucotoxicity, and enhanced flux through this pathway could contribute to the development of insulin resistance, insulin secretory dysfunction, diabetic complications, and obesity. In addition, the hexosamine pathway appears to be involved in the development of diabetic complications (306). Glycosylation modifies activity of nuclear and cytoplasmic proteins, for example endothelial nitric oxide synthase (307), PKC (308), and pathways involved in PKA (309) or insulin signaling (310), all potentially contributing to endothelial dysfunction (307, 311). In glomerular epithelial and mesangial cells from nephropathic kidneys (312) and in atherosclerotic plaques of diabetic patients (310), there is increased glycosylation. Thus, activation of the hexosamine pathway

may explain, in part, the increased risk of vascular disease in diabetic patients.

IV. Conclusion

There are both environmental and genetic factors that must account for the epidemic increase in rates of type 2 diabetes occurring in the United States and worldwide. The pathophysiology of the disorder clearly involves both insulin resistance and relative insulin deficiency. Although extensive efforts have been made in genomic searches and in the evaluation of the structure and function of genes and proteins involved in insulin secretion and action, no single gene or protein appears to be causative in the development of common type 2 diabetes. Monogenetic defects have only been identified in rare syndromes of extreme insulin resistance or patients with MODY. It is likely that the common disorder is heterogeneous, such that multiple defects are necessary and permissive to the development of hyperglycemia. It is now important to consider the contribution of metabolic pathways other than direct insulin signaling and the role of key regulators that coordinate metabolic pathways in the development of hyperglycemia if we are to gain additional insights into the disease and discover new targets for primary preventative or therapeutic pharmacological interventions.

Despite the important role of insulin resistance in the development of diabetes, extensive research efforts over the last decade have revealed much information on insulin signaling without determining the cause of most cases of diabetes. Because glycemia is determined by both insulin-dependent and insulin-independent mechanisms of glucose clearance from the circulation, to better understand the disease it is important to carefully consider the cellular fates of glucose. Dysregulation of multiple steps in glucose clearance could then contribute in an additive or synergistic way to the development of hyperglycemia. Much previous work focused on the rate-limiting enzymes of a given pathway, and such work did identify alterations of glucokinase to directly cause diabetes in a small subset of patients with MODY. However, the strategy of evaluating rate-limiting enzymes to identify the molecular cause of diabetes in most cases has not been productive in more typical or common diabetes. One possible mechanism for the coordinated dysregulation of several pathways or components of a single pathway could be through alterations in transcription factors or transcription factor regulating proteins. If true, this could account for the findings of any protein along a single metabolic pathway to be altered in only a small and statistically insignificant way when assessed through typical physiology studies. However, defects in the coordinated regulation of the entire metabolic pathway or several pathways simultaneously could ultimately contribute in a meaningful way to the development of type 2 diabetes. With the genomic and proteomic tools now available, increasing numbers of transcription factors and regulators are being identified. Improved understanding of the pathways of glucose metabolism could permit a greater understanding of the contribution that changes in these proteins could have in the pathogenesis of this disease. Ultimately, a better understanding of the pathophysiology of type 2 diabetes will aid the development of new and complementary drug targets.

Acknowledgments

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