Minireview

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Chronic Oxidative Stress as a Central Mechanism for Glucose Toxicity in Pancreatic Islet Beta Cells in Diabetes*

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R. Paul Robertson‡

From the Pacific Northwest Research Institute, Seattle, Washington 98122 and the Departments of Medicine and Pharmacology, University of Washington, Seattle, Washington 98122

Glucose in chronic excess causes toxic effects on structure and function of organs, including the pancreatic islet. Multiple biochemical pathways and mechanisms of action for glucose toxicity have been suggested. These include glucose autoxidation, protein kinase C activation, methylglyoxal formation and glycation, hexosamine metabolism, sorbitol formation, and oxidative phosphorylation. There are many potential mechanisms whereby excess glucose metabolites traveling along these pathways might cause beta cell damage. However, all these pathways have in common the formation of reactive oxygen species that, in excess and over time, cause chronic oxidative stress, which in turn causes defective insulin gene expression and insulin secretion as well as increased apoptosis. This minireview provides an overview of these mechanisms, as well as a consideration of whether antioxidant strategies might be used to protect further deterioration of the beta cell after the onset of diabetes and hyperglycemia.

Diabetes mellitus is a disease characterized by hyperglycemia and is caused by absolute or relative insulin deficiency, sometimes associated with insulin resistance. It has multiple etiologies and segregates into two major forms. Type 1 diabetes is an autoimmune disease in which the patient's own immune system reacts against islet antigens and destroys the beta cell. Type 2 diabetes is a polygenic syndrome with multiple etiologies rather than a single specific disease. As the hyperglycemia of diabetes becomes chronic, the sugar that normally serves as substrate, fuel, and signal takes on the darker role of toxin. Chronic hyperglycemia is the proximate cause of retinopathy, kidney failure, neuropathies, and macrovascular disease in diabetes. The beta cell in type 2 diabetes is also adversely affected by chronic hyperglycemia and, in this sense, is also a target for secondary complications. As hyperglycemia worsens, the beta cell steadily undergoes deterioration, secretes less and less insulin, and becomes a participant in a downward spiral of loss of function. This relentless deterioration in cell function caused by constant exposure to supraphysiologic concentrations of glucose is termed glucose toxicity.

Mechanisms of Hyperglycemia-induced Oxidative Stress

In physiologic concentrations, endogenous reactive oxygen species (ROS)[1] help to maintain homeostasis. However, when ROS accumulate in excess for prolonged periods of time, they cause chronic oxidative stress and adverse effects. This is particularly relevant and dangerous for the islet, which is among those tissues that have the lowest levels of intrinsic antioxidant defenses. Multiple biochemical pathways and mechanisms of action have been implicated in the deleterious effects of chronic hyperglycemia and oxidative stress on the function of vascular, retinal, and renal tissues. Considerably less work has been performed using islet tissue. At least six pathways are emphasized in the literature as being major contributors of ROS. Each will be considered briefly.

Glyceraldehyde Autoxidation—Glyceraldehyde 3-phosphate is a phosphorylation product formed from glucose during anaerobic glycolysis. The partner product, dihydroxyacetone phosphate, also contributes to intracellular glyceraldehyde concentrations via enzymatic conversion by triose-phosphate isomerase. Thereafter, glyceraldehyde 3-phosphate is oxidized by glyceraldehyde-phosphate dehydrogenase (GAPDH). Continuance of glycolysis yields pyruvate, which enters the mitochondria where it is oxidized to acetyl-CoA, and the processes of the tricarboxylic acid cycle and oxidative phosphorylation begin.

One alternative to this classic pathway of glucose metabolism is the less familiar route of glyceraldehyde autoxidation (Fig. 1, *pathway 1*). The potential relevance of this pathway to diabetes mellitus was pointed out by Wolff and Dean (1), who emphasized that autoxidation of α-hydroxyaldehydes generates hydrogen peroxide (H_2O_2) and α-ketoaldehydes. In the presence of redox active metals, H_2O_2 can form the highly toxic hydroxyl radical. This pathway, therefore, forms two potentially toxic substances, α-ketoaldehydes, which contribute to glycosylation-related protein chromophore development, and the hydroxyl radical, a reactive oxygen species that can cause mutagenic alterations in DNA. Although glyceraldehyde is characteristically thought of as an insulin secretagogue, when present in excess it may also inhibit insulin secretion (2). Long term exposure to high glucose concentrations decreases GAPDH activity in islets (3), which favors excess glyceraldehyde accumulation. Exposure of endothelial cells to 30 mM glucose caused GAPDH inhibition (4) through the mechanism of ROS-activated poly(ADP-ribosyl)ation of GAPDH by poly-(ADP-ribose) polymerase. This in turn was associated with intracellular advanced glycation end product (AGE) formation and activation of PKC, the hexosamine pathway, and NF-κB.

PKC Activation—Dihydroxyacetone can undergo reduction to glycerol 3-phosphate and acylation and thereby increase *de novo* synthesis of diacylglycerol, which activates protein kinase C, of which there at least 11 isoforms (Fig. 1, *pathway 2*). Activation of PKC has many biochemical consequences that relate to microvascular disease in diabetes. PKC activation is associated with increases in TGF-β1, vascular endothelial

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‡ To whom correspondence should be addressed: Pacific Northwest Research Institute, 720 Broadway, Seattle, WA 98122. Tel.: 206-726-1210; Fax: 206-726-1217; E-mail: rpr@pnri.org.

[1] The abbreviations used are: ROS, reactive oxygen species; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; AGE, advanced glycation end product; PKC, protein kinase C; TGF, transforming growth factor; GFAT, glutamine:fructose-6-phosphate aminotransferase; SOD, superoxide dismutase; ZDF, Zucker diabetic fatty; JNK, c-Jun NH_2-terminal kinase; γ-GCL, γ-glutamylcysteine ligase.

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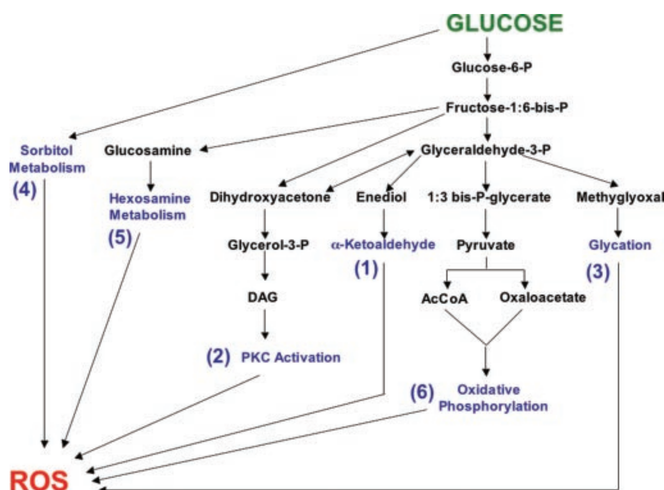

FIG. 1. **Six biochemical pathways along which glucose metabolism can form ROS.** Under physiologic conditions, glucose primarily undergoes glycolysis and oxidative phosphorylation (6). Under pathologic conditions of hyperglycemia, excessive glucose levels can swamp the glycolytic process and inhibit glyceraldehyde catabolism, which cause glucose, fructose-1,6-bisphosphate, and glyceraldehyde-3-P to be shunted to other pathways: *1*, enolization and α-ketoaldehyde formation; *2*, PKC activation; *3*, dicarbonyl formation and glycation; *4*, sorbitol metabolism; *5*, hexosamine metabolism; and *6*, oxidative phosphorylation. *DAG*, diacylglycerol.

growth factor, endothelin-1, NAD(P)H oxidase, NF-κB, and ROS (5–7).

Methylglyoxal, Glycation, and Sorbitol—Three reactive intracellular dicarbonyls (glyoxal, methylglyoxal, and 3-deoxyglucosone) form AGEs by reacting with amino groups on intracellular and extracellular proteins (8) (Fig. 1, *pathways 3* and *4*). AGEs play important roles in the pathogenesis of secondary complications of diabetes, especially with regard to microvascular disease in the retina, nerves, and kidney and likely islets. When GAPDH-mediated catabolism of glyceraldehyde-3-P is impaired, such as in the presence of high glucose concentrations, accumulation of glyceraldehyde-3-P and dihydroxyacetone favors formation of methylglyoxal. Additionally, increased flux along the polyol pathway as a result of hyperglycemia results in aldose reductase-mediated NADPH-dependent reduction of glucose to form sorbitol. Oxidation of sorbitol by NAD^+ increases the cytosolic NADH:NAD^+ ratio, which tends to inhibit GAPDH activity. This can lead to increased levels of triose phosphates, methylglyoxal, and diacylglycerol. This chain of events is also associated with consumption of NAD^+ by activated poly(ADP-ribose) polymerase, which can be activated by hyperglycemia via increased production of ROS and DNA strand breaks (4). Above and beyond the damage that reactive dicarbonyls can cause through enhancement of glycation and the formation of AGEs, the Maillard reaction between carbohydrates and proteins also generates ROS (9). Thus, hyperglycemia simultaneously enhances both glycative and oxidative stress, which together synergistically contribute to the development of diabetic complications.

Hexosamine Pathway—In states of excess intracellular glucose, fructose 6-phosphate via glutamine:fructose-6-phosphate aminotransferase (GFAT) can form glucosamine 6-phosphate and then UDP-*N*-acetylglucosamine, which supports proteoglycan synthesis and the formation of (*O*)-linked glycoproteins (Fig. 1, *pathway 5*). This pathway has been shown to be related to increases in transcription of TGF-α, TGF-β1, and PAI-1 and has been implicated in insulin resistance (5, 10). Glucosamine infusions in rodents and in humans have been associated with interference with glucose sensing by the beta cell and with insulin sensitivity (11). Adenovirus-mediated overexpression of GFAT was reported to impair glucose-stimulated insulin secretion and to reduce expression levels of the insulin, GLUT2, and glucokinase genes (12). The DNA binding activity of PDX-1, a critical transcription factor for these genes, was also markedly reduced. In these experiments glucosamine was found to increase hydrogen peroxide levels, and the antioxidant *n*-acetylcysteine prevented the adverse effects of GFAT overexpression.

Oxidative Phosphorylation—High glucose concentrations increase the mitochondrial proton gradient as a result of overproduction of electron donors by the tricarboxylic acid cycle, which in turn increase production of mitochondrial superoxide (13) (Fig. 1, *pathway 6*). In these experiments, inhibition by Mn-SOD or UCP-1 of hyperglycemia-induced overproduction of mitochondrial superoxide prevented the increases in polyol pathway flux, intracellular AGE formation, PKC activation, and hexosamine pathway activity in endothelial cells. High glucose concentrations were shown to increase mitochondrial superoxide production, proton leak, lower ATP levels, and impaired glucose-induced insulin secretion in islets from wild type but not from UCP-2-knock-out animals (14), suggesting that superoxide-mediated activation of UCP-2 could play a role in type 2 diabetes. It has also been reported that a 2 mM glyceraldehyde concentration in 24-h islet incubations increased ROS levels and inhibited insulin secretion, effects that were abrogated by *n*-acetylcysteine (15). However, in these studies neither inhibitors of mitochondrial oxidative phosphorylation nor adenovirus overexpression of Mn-SOD prevented the ability of glyceraldehyde to increase islet reactive oxygen species levels. 2 mM glyceraldehyde has been reported to increase intraislet glyceraldehyde concentrations to a level similar to that achieved with 20 mM glucose (16). Thus, when the glycolytic pathway is swamped by glucose, it seems likely that both mitochondrial and non-mitochondrial pathways contribute ROS to the glucotoxic process that impairs beta cell function.

Consequences of Oxidative Stress on Beta Cell Function

At the root of the relentless decline in beta cell function found in the glucotoxic state is abnormal insulin gene expression as well as decreases in insulin content and insulin secretion. These deleterious effects of glucose toxicity also converge with the adverse consequences of lipotoxicity, both of which can cause increased islet apoptosis.

Effects of Chronic Oxidative Stress on Insulin Gene Expression—Chronic exposure of the beta cell to supraphysiologic concentrations of glucose causes defective insulin gene expression accompanied by marked decreases in insulin content and abnormal insulin secretion (17). The defect in insulin gene expression is due to the loss of at least two critical proteins that activate the insulin promoter (Fig. 2). One is PDX-1 (18, 19), and the other is RIPE-3b1 activator (20), recently identified as MafA (21–24). MafA binding to the insulin promoter disappears 20 passages earlier than PDX-1 binding in experiments with glucotoxic HIT-T15 cells. In our laboratory transient transfection of glucotoxic HIT-T15 cells with PDX-1 cDNA partially reconstitutes insulin promoter activity (25), and combinatorial transfection with both PDX-1 and MafA completely normalizes insulin promoter activity.[2] Glucotoxicity experiments using the αTC-1/9 cell indicated no abnormalities in glucagon gene expression or glucagon secretion (26). Isolated islets chronically exposed to high glucose concentrations also reveal decreased insulin gene expression and insulin secretion (27–29).

In vivo experiments with the Zucker diabetic fatty (ZDF) rat substantiated the findings of defective insulin gene expression in the glucotoxic state. Development of hyperglycemia in this

[2] J. S. Harmon, R. Stein, and R. P. Robertson, unpublished results.

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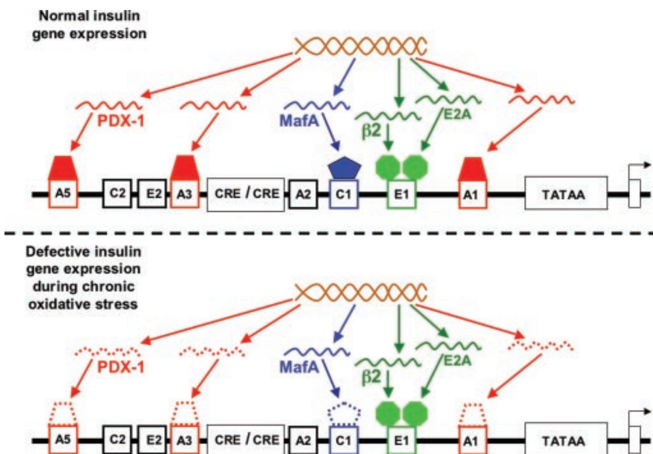

FIG. 2. **The glucotoxic effect on insulin gene expression via loss of PDX-1 and MafA.** These two transcription factors are essential to normal levels of insulin promoter activity. Chronic exposure of beta cells to excess glucose and ROS levels cause loss of PDX-1 gene expression, loss of MafA protein, and no change in β2 or E2A binding to the promoter. Consequently, diminished insulin synthesis, decreased insulin content, and defects in insulin secretion ensue.

animal model is accompanied by loss of insulin gene expression and islet PDX-1 mRNA (30). Prolonged exposure to high glucose concentrations also up-regulated levels of the transcription factor C/EBPβ, a repressor for insulin promoter activity (31, 32). Decreases in PDX-1 binding to the insulin promoter caused by oxidative stress were reported to be preceded by activation of JNK and dominant negative JNK overexpression preserved insulin gene expression under hyperglycemic conditions (33).

Relationships between Glucose Toxicity and Lipotoxicity—The clinical state of diabetes mellitus is often accompanied by elevated blood levels of cholesterol, triglyceride, and free fatty acids. This gave rise to the consideration that deteriorating beta cell function in diabetic patients might be caused by chronic exposure to high concentrations of lipids, a concept termed the lipotoxicity hypothesis (34). Prolonged exposure of pancreatic beta cells to fatty acids has been reported to inhibit insulin gene expression (35). A prominent hypothesis is that the simultaneous presence of hyperglycemia and elevated fatty acid levels causes accumulation of cytosolic citrate, the precursor of malonyl-CoA, which inhibits carnitine palmitoyltransferase-1, the enzyme responsible for fatty acid transport into the mitochondrion (36). This model envisions that, in the presence of high glucose concentrations, elevated fatty acids are not readily oxidized in mitochondria but are shunted toward esterification pathways. Pertinent to this model are the observations that the adverse effects of palmitate on insulin gene expression and secretion were seen only when beta cells were simultaneously exposed to high concentrations of glucose and that palmitate-induced accumulation of beta cell triglycerides occurred only in the presence of high glucose (35). These *in vitro* findings suggest that lipotoxicity requires antecedent hyperglycemia but that glucose toxicity occurs independent of lipotoxicity.

To differentiate *in vivo* between hyperlipidemia and hyperglycemia as the cause of islet triglyceride accumulation and defective insulin gene expression in ZDF rats, animals were treated with either the lipid-lowering drug bezafibrate or the blood glucose-lowering agent phlorizin (37). Islet triglyceride content was decreased and insulin gene expression was preserved by phlorizin but not by bezafibrate treatment, indicating that islet triglyceride accumulation requires hyperglycemia. More recent studies examining the mechanism of action whereby palmitate inhibits insulin gene expression revealed that the palmitate-induced decrease in insulin gene expression was associated with inhibition of insulin promoter activity and increased levels of intracellular ceramide (38).

Apoptosis—Increased apoptosis was found when islets were cultured in 16.7 mM glucose as compared with islets cultured in 5.5 mM glucose or 11 mM mannitol + 5 mM glucose (39). The antiapoptotic gene *Bcl-2* was unaffected by these conditions whereas *Bcl-xL* was reduced. The proapoptotic genes *Bad*, *Bid*, and *Bik* were overexpressed in the islets maintained in high glucose concentrations. Loss of beta cell mass resulting from an increase in beta cell death was reported to be an important contributor to the evolution of the diabetic state in ZDF rats (40). Palmitate-induced generation of ceramide has been reported to lead to apoptosis (34). However, in other studies *de novo* ceramide synthesis was not required for palmitate-induced apoptosis because inhibitors of *de novo* ceramide synthesis did not block palmitate-induced apoptosis and palmitate-induced apoptosis occurred in mutant CHO cells deficient in *de novo* ceramide synthesis (41). These experiments also revealed that palmitate-induced apoptosis causes generation of ROS and that this is inhibited by antioxidants, which simultaneously blocked caspase-3 activity. This suggests a primary role for ROS in the induction of apoptosis by palmitate.

Antioxidant Strategies to Protect the Beta Cell from Hyperglycemia

The theme of this minireview is that continuation of high glucose levels after onset of either type 1 or type 2 diabetes has secondary adverse effects on the beta cell itself, not that glucose toxicity is the initial cause of either disease. In the case of type 1 diabetes it has been published that increased glucose levels are associated with increased beta cell generation of cytokines (42), which are prooxidants. In a model of type 2 diabetes, high glucose concentrations increased intracellular peroxide levels in islets (43). This raises questions about the state of antioxidant host defenses within the islet and whether augmentation of these defenses might be an appropriate therapeutic strategy to lessen the impact of diabetes and hyperglycemia on the beta cell.

Beta Cell Host Mechanisms against Chronic Oxidative Stress—Clinical reports of elevated levels of oxidative stress markers in patients with type 2 diabetes are numerous. Unfortunately, the islet is among the least well endowed tissues in terms of intrinsic antioxidant enzyme expression, including SOD-1, SOD-2, catalase, and glutathione peroxidase (44, 45). In contrast, gene expression of γ-glutamylcysteine ligase, the rate-limiting enzyme for glutathione synthesis, is well represented in islets. In our laboratory the levels of γ-GCL mRNA are comparable with those found in liver and greater than those found in muscle, lung, and fat.[3] Long term exposure to high glucose conditions decreases γ-GCL expression in mesangial as well as retinal cells, and this is associated with a decrease in glutathione levels (46, 47). Thus, type 2 diabetes mellitus is associated with elevated markers of chronic oxidative stress, pancreatic islets contain relatively low levels of antioxidant gene expression, and elevated glucose levels down-regulate the rate-limiting enzyme for glutathione synthesis.

Beneficial Effects of Antioxidant Enzyme Overexpression in Islets—Injections of superoxide dismutase have been reported to act prophylactically against alloxan-induced diabetes (48). Transgenic animals overexpressing superoxide dismutase have

[3] P. O. T. Tran, S. M. Parker, E. LeRoy, C. C. Franklin, T. J. Kavanagh, E. Oseid, T. Zhang, J. S. Harmon, and R. P. Robertson, unpublished results.

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enhanced beta cell tolerance to oxidative stress-induced diabetes (49). Overexpression of antioxidant enzymes in beta cell lines provide protection against prooxidants, and combinatorial rather than single overexpression of antioxidant enzymes is more efficacious (50). Transgenic overexpression of catalase provided protection for the beta cell against streptozotocin and hydrogen peroxide (51). Adenovirus overexpression of catalase and superoxide dismutase has been shown to protect human islets (52, 53) and a beta cell line (54) against oxidative stress. In our laboratory adenoviral overexpression of glutathione peroxidase (43) and γ-GCL[3] have been shown to protect islets against the adverse consequences of prooxidants on insulin gene expression, insulin content, and insulin secretion.

Protection by Antioxidant Drugs against Beta Cell Oxidative Stress—Several antioxidant drugs have been evaluated as protectors against beta cell oxidative stress. *N*-Acetylcysteine protects against oxidative stress and diabetes in ZDF rats and db/db mice (55, 56). In both instances, this drug provided preserved insulin content and insulin gene expression as well as PDX-1 binding to the insulin promoter. The oral hypoglycemic agents metformin and troglitazone have antioxidant properties and prevent hyperglycemia in the ZDF rat (30, 57). Vitamin E has beneficial effects on glycemic control in GK rats (58). Gliczide, a commonly used sulfonylurea used in the treatment of type 2 diabetes, has been shown to protect pancreatic beta cells from damage by hydrogen peroxide (59). These findings suggest that adjunct therapy with antioxidants may represent a useful ancillary pharmacologic approach to the management of type 2 diabetes.

Conclusion

One potential central mechanism for glucose toxicity is the formation of excess ROS levels, which takes place within multiple mitochondrial and non-mitochondrial pathways. The islet is especially vulnerable to ROS because of its low intrinsic level of antioxidant enzymes. Chronically excessive glucose and ROS levels can cause decreased insulin gene expression via loss of the transcription factors PDX-1 and MafA and can also accelerate rates of apoptosis. This pathophysiologic sequence sets the scene for considering antioxidant therapy as an adjunct in the management of diabetes.

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