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Commentary

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Diabetes, microvascular complications, and cardiovascular complications: what is it about glucose?

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Glycemic control is the primary mediator of diabetic microvascular complications and also contributes to macrovascular complications. A new study (see related article beginning on page 1049) reveals a previously unrecognized association between oxidant activation of poly(ADP ribose) polymerase (PARP) and upregulation of known mediators of glycemic injury. Inhibitors of PARP may have potential therapeutic roles in the prevention of diabetic complications.

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The prevalence of obesity, diabetes, and the metabolic syndrome is increasing in the US and worldwide at astonishing rates (1, 2). Diabetes is the leading cause of blindness, renal failure, and amputation in the United States. These conditions can be slowed or prevented with optimal glycemic control (3, 4). Accompanying the diabetes epidemic is a concomitant two- to four-fold excess risk for cardiovascular disease (5, 6). Modification of traditional cardiovascular risk factors has an impressive impact on morbidity and mortality in subjects with diabetes and insulin resistance as reported in various studies, including the Scandinavian Simvastatin Survival Study (7, 8), the Cholesterol and Recurrent Events (CARE) study (9), the MRC/BHF Heart Protection Study (10), the Steno-2 study (11), the Losartan Intervention For Endpoint reduction in hypertension study (12; known as LIFE), and the Heart Outcomes Prevention Evaluation study (13; known as HOPE). Even

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Nonstandard abbreviations used: advanced glycation end product (AGE); reactive oxygen species (ROS); poly(ADP-ribose) polymerase (PARP).

with these effective interventions, people with diabetes still have increased morbidity and mortality when compared to the nondiabetic population. The question remains, what is it about diabetes (defined by high blood glucose levels) that leads to excess vascular risk? In this issue of the *JCI*, Du and colleagues present a new molecular target – poly(ADP ribose) polymerase (PARP) – dysregulated by hyperglycemic injury, which may have implications for prevention of both microvascular disease and macrovascular disease because this enzyme affects critical targets in the endothelial cell (14).

Diabetic complications and glucose

Glucose is the driving force in microvascular complications of diabetes, yet the action of glucose alone seems inadequate and unable to account for the excess atherosclerosis observed in subjects with diabetes. In type 2 diabetes, insulin resistance, and the metabolic syndrome, the vasculature is exposed to a frontal assault by hypertension, dyslipidemia (increased triglycerides, low HDL and high LDL cholesterol), inflammation, and impaired fibrinolysis (5, 6). This toxic metabolic environment increases atherosclerotic risk in persons with the metabolic syndrome. The heightened risk observed in the metabolic syndrome inevitably sets the stage for increased vascular disease in type 2

diabetics, but hyperglycemia adds additional risk.

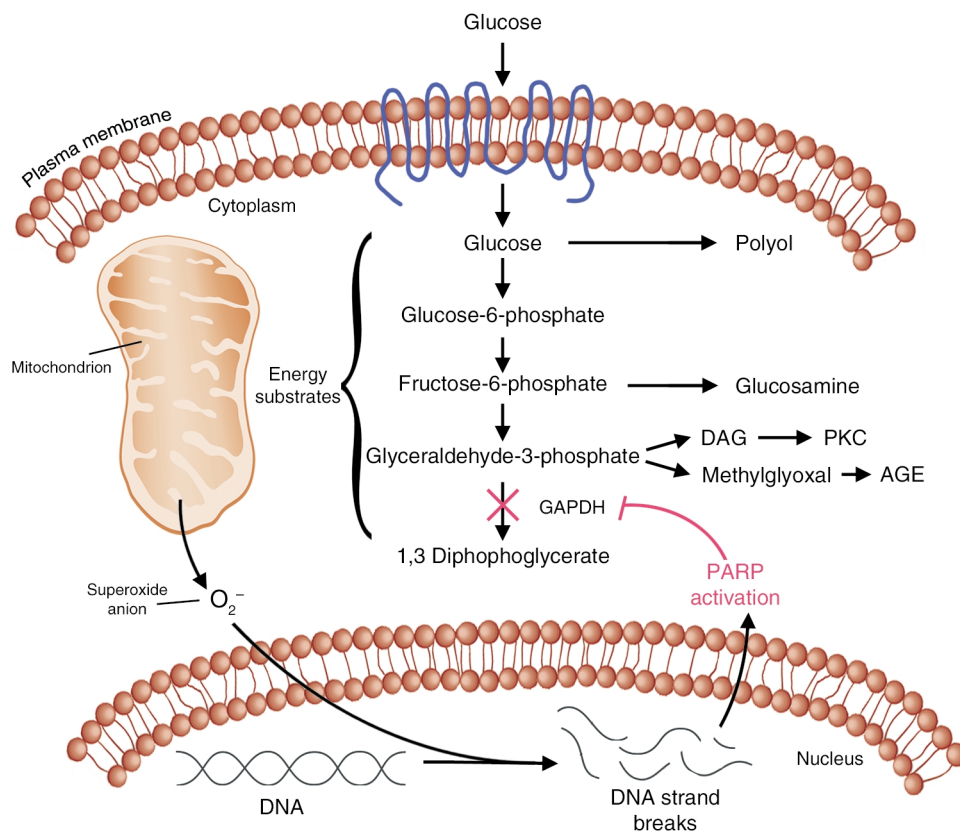
Strong epidemiological evidence suggests a correlation among glucose, atherosclerotic plaque burden, cardiovascular events, and increased morbidity and mortality (15–17). In an autopsy study of 18- to 34-year-olds there was an increase in atherosclerotic plaque burden in subjects with elevated hemoglobin A1C (17). The Honolulu Heart Program demonstrated a predictive correlation between fasting plasma glucose levels (nondiabetic, impaired glucose tolerance, and diabetic ranges) and cardiovascular events and mortality (18). Large population studies from Northern Europe indicate a direct correlation between glycemic control (as measured by glycohemoglobin) and cardiovascular morbidity and mortality (16, 19). As will be discussed later, hyperglycemia has specific deleterious effects upon vascular endothelial function that could account for these epidemiological correlations between hyperglycemia and poor vascular outcomes. One would predict, based upon epidemiological data, that interventional studies targeting hyperglycemia would show improved cardiovascular outcomes. To date, no such compelling evidence has emerged. In fact, in the largest prospective glucose-lowering trial in type 2 diabetes patients, the United Kingdom Prospective Diabetes Study (4), there were no statistical improvements in cardiovascular outcomes when glucose was lowered using insulin or sulfonylureas. Only in the small metformin cohort ($n = 342$) were cardiovascular outcomes improved by optimal glycemic control. A few small studies have suggested a positive impact of glycemic control on cardiovascular events, but this point remains highly debated. The conclusions of a recent panel convened by the American Heart Association suggest that while glycemia contributes to cardiovascular risk, treatment of glycemia, exclusive of other potent cardiovascular risk factor intervention, is inadequate to reverse or reduce the complex atherosclerotic process (18).

Mechanism of glucotoxicity

The negative impact of hyperglycemia on endothelial function and patho-

Figure 1

High glucose flux through constitutive glucose transporters on endothelial cells overwhelms the mitochondrial electron transport system. Excess mitochondrial substrate flux results in the generation of reactive oxygen species that cause DNA strand breaks and activation of PARP. PARP ribosylates and inactivates GAPDH, thereby disrupting normal glucose metabolism. Inactivation of GAPDH effectively shunts glucose into the polyol pathway and leads to activation of PKC and accumulation of AGEs and glucosamine. DAG, diacylglycerol.



logical changes observed in diabetes is supported in the literature (reviewed in refs. 20, 21). Endothelial cells in vitro are exquisitely sensitive to high glucose (25mM). Nishikawa et al. (21) and others have carefully characterized four major molecular signaling mechanisms activated by hyperglycemia in endothelial cells and other cell types vulnerable to hyperglycemic injury. These include activation of PKC (via diacylglycerol), increased hexosamine pathway flux, increased advanced glycation end product (AGE) formation, and increased polyol pathway flux. Nishikawa et al. recently proposed the existence of a unifying mechanism that integrates the above pathways: increased production of reactive oxygen species (ROS) (specifically superoxide) by the mitochondrial electron transport chain (21). In their original report, numerous theoretical constructs were outlined for the impact of altered redox state upon formation of polyols, AGEs, and PKC. What remained unclear were the downstream targets of oxidant stress. In the paper by Du et al. (14) in this issue of the *JCI*, this group takes their seminal

observation one step further and defines one consequence of increased ROS, namely activation of PARP. PARP activation leads to ribosylation and inactivation of GAPDH. Inhibition of GAPDH increases delivery of glycolytic intermediates to the mitochondria. This change in turn would be expected to increase mitochondrial superoxide production and also to increase flux through the AGE and PKC glucotoxic pathways (Figure 1).

Implications for therapy

It has been well established that diabetes leads to microvascular complications, and it has also been suggested that hyperglycemia plays an accelerating role in macrovascular disease. This excess disease burden is driven by glucose-related activation of PKC, accumulation of AGEs, excess polyol flux, and accumulation of glucosamine (20, 22–25). Interventions for each of these mechanisms have had great efficacy in animal models but disappointing outcomes in clinical trials (26). It was concluded that a cocktail of inhibitors might be necessary to effectively block these deleterious cellular responses in

a complex human model of fluctuating hyperglycemia (20). The observation that these pathways reflect a single hyperglycemia-induced process, namely oxidative stress, suggested that antioxidants could serve as a single agent in the prevention of diabetes complications. To date, human studies with α lipoic acid suggest a therapeutic benefit (27, 28), but the use of conventional antioxidants has been disappointing in larger trials (29). Conventional antioxidants scavenge free radicals in an inefficient stoichiometric manner so that one molecule of the antioxidant would be needed to neutralize each free radical generated. Novel small molecular weight compounds that function as superoxide dismutase mimetics may offer more reliable benefits due to the catalytic properties that could permit enzymatic detoxification (30). The observation that PARP drives glucotoxicity through inhibition of GAPDH suggests PARP inhibitors as another therapeutic tool for complication prevention. In theory, these agents could have an effect equivalent to combination inhibitor therapy due to positive

effects on AGE, PKC, and NF- κ B. Indeed, the few reports employing PARP inhibitors in animal models of diabetes support the therapeutic potential of these agents (31, 32). With the incidence of diabetes and its complications on the rise, these results offer hope for new treatments in the foreseeable future.

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