Am J Physiol Heart Circ Physiol 310: H153–H173, 2016.
First published October 30, 2015; doi:10.1152/ajpheart.00206.2015.

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Damaging effects of hyperglycemia on cardiovascular function: spotlight on glucose metabolic pathways

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Submitted 19 March 2015; accepted in final form 27 October 2015

Mapanga RF, Essop MF. Damaging effects of hyperglycemia on cardiovascular function: spotlight on glucose metabolic pathways. *Am J Physiol Heart Circ Physiol* 310: H153–H173, 2016. First published October 30, 2015; doi:10.1152/ajpheart.00206.2015.—The incidence of cardiovascular complications associated with hyperglycemia is a growing global health problem. This review discusses the link between hyperglycemia and cardiovascular diseases onset, focusing on the role of recently emerging downstream mediators, namely, oxidative stress and glucose metabolic pathway perturbations. The role of hyperglycemia-mediated activation of nonoxidative glucose pathways (NOGPs) [i.e., the polyol pathway, hexosamine biosynthetic pathway, advanced glycation end products (AGEs), and protein kinase C] in this process is extensively reviewed. The proposal is made that there is a unique interplay between NOGPs and a downstream convergence of detrimental effects that especially affect cardiac endothelial cells, thereby contributing to contractile dysfunction. In this process the AGE pathway emerges as a crucial mediator of hyperglycemia-mediated detrimental effects. In addition, a vicious metabolic cycle is established whereby hyperglycemia-induced NOGPs further fuel their own activation by generating even more oxidative stress, thereby exacerbating damaging effects on cardiac function. Thus NOGP inhibition, and particularly that of the AGE pathway, emerges as a novel therapeutic intervention for the treatment of cardiovascular complications such as acute myocardial infarction in the presence hyperglycemia.

cardiovascular diseases; hyperglycemia; hexosamine biosynthetic pathway; advanced glycation end products; polyol pathway

THERE IS A STRONG LINK BETWEEN diabetes and a severalfold greater risk for the onset of cardiovascular diseases (CVD) (18, 42, 271) such as stroke (250), atrial fibrillation, flutter, coronary heart disease, and left ventricular hypertrophy (207). For example, type 2 diabetes is strongly associated with arterial disease because it is usually coupled to the metabolic syndrome that is characterized by hypertension, high blood sugar levels, excess abdominal fat, and dyslipidemia, which can precipitate vascular endothelial dysfunction and accelerate atherosclerosis (18, 247, 305). Acute myocardial infarction is the major contributor to cardiovascular mortality with diabetes and often progresses to end-stage heart failure (77, 151, 300). The presence of myocardial dysfunction in the absence of coronary artery disease and hypertension ("diabetic cardiomyopathy") can also occur, with hyperglycemia considered to be a major contributing factor (22, 78, 93). This condition is characterized by diastolic and systolic dysfunction, typically manifesting with prolonged ventricular muscle relaxation and reduced compliance (8) that usually lead to heart failure. Although some strides have been made to better understand the effect of hyperglycemia on CVD onset, the mechanisms responsible for initiating and propagating macro- and microvascular damage remain unclear and controversial. This review therefore aims to provide unique insights into this intriguing question by specifically evaluating the role of oxidative stress and downstream activation of nonoxidative glucose pathways (NOGPs) as significant contributors to the development of hyperglycemia-induced CVD onset.

Hyperglycemia-Induced Actation of the NOGPs

How are the NOGPs activated in response to hyperglycemic conditions? The widely accepted "unifying hypothesis of diabetes" proposed by Brownlee (38) centers around the detrimental effects of hyperglycemia-mediated mitochondrial superoxide generation. The prevailing hypothesis is that hyperglycemia-induced increases in electron transfer donors (NADH and $FADH_2$) enhance electron flux through the mitochondrial electron transport chain. This in turn causes the inner mitochondrial membrane potential to rise above a threshold value

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that results in greater production of reactive oxygen species (ROS) (163, 266). The relatively high electrochemical potential can also lead to incomplete inhibition of electron transport in complexes I and III, resulting in an accumulation of electrons in coenzyme Q that drives the partial reduction of molecular oxygen to generate mitochondrial superoxide (37, 82, 83). The ROS produced in the process can also damage the respective respiration complex itself and further decrease its activity, thereby exacerbating free radical production (224, 344). In addition, hyperglycemia-mediated glycation of complex III proteins can further contribute to increased mitochondrial superoxide production with diabetes (251).

The proposal is made that excess mitochondrial superoxide availability elicits genotoxic effects in the nucleus that lead to increased poly(ADP-ribosyl)ation as a defensive measure to counteract DNA damage. The poly(ADP-ribose) polymerase (PARP)-1 isoform (21, 41, 203) fulfills this role in the heart by functioning as a DNA damage sensor and signaling molecule that is able to bind both single- and double-stranded DNA breaks. PARP-1 catalyzes the formation of ADP-ribose from NAD^+ by cleavage of the glycosidic bond between nicotinamide and ribose (21, 41). Glutamate, aspartate, and carboxy-terminal lysine residues of target or "acceptor" proteins are then covalently modified by the addition of an ADP-ribose subunit via formation of an ester bond. It is further postulated that the glycolytic enzyme GAPDH subsequently translocates to the nucleus where poly(ADP-ribosyl)ation lowers its activation (21, 41).

It is plausible that the inhibitory effect of (ADP-ribosyl)ation on GAPDH represents a feedback loop to reduce glycolysis and transiently limit metabolite flux into mitochondria, thereby decreasing reducing equivalents and mitochondrial ROS overproduction (209). Attenuated GAPDH activity subsequently results in the upstream accumulation of glycolytic metabolites that are shunted into the various NOGPs [i.e., the polyol pathway, formation of advanced glycation end products (AGEs), the hexosamine biosynthetic pathway (HBP), and activation of protein kinase C (PKC)] (Fig. 1) (165, 220, 315). Such pathway activation can then further exacerbate oxidative stress and trigger damaging outcomes, thereby contributing to micro- and macrovascular complications associated with diabetes. In support, the normalization of mitochondrial ROS levels prevented high glucose-mediated NOGP activation in vascular endothelial cells (214).

The unifying concept was further expanded upon by other scholars who also implicated reactive nitrogen species in this process (222, 223, 279), in which increased peroxynitrite levels can lead to DNA strand breaks and PARP activation (41, 62, 79) while lowering GAPDH activity by covalent modification of an active thiol site (279, 306). Although the unifying theory—with a strong emphasis on excess mitochondrial superoxide as a primary causative agent—has several strengths, there are still some unanswered questions such as the role of multiple sources of intracellular oxidative stress. The precise nature and interactions among mitochondrial and extramitochondrial sources of ROS are also not entirely clear, although we recently proposed that high-glucose availability results in the generation of relatively small amounts of "trigger" mitochondrial ROS in heart cells that subsequently activate NADPH oxidase isoforms to further elevate intracellular ROS levels (147). These data are consistent with other information that implicates NADPH oxidase and uncoupled endothelial nitric oxide synthase (eNOS) as more immediate, downstream targets of hyperglycemia (15, 170, 172, 177).

There is also supporting evidence that enhanced ROS generation from nonmitochondrial sources may precipitate increased oxidative stress (101, 347). This includes NADPH oxidase, glucose autoxidation, lipoxygenases, cyclo-oxygenases, peroxidases, heme proteins, xanthine oxidase, peroxisomes, uncoupled eNOS, and the vascular *P*-450 microsomal detoxifying system (52, 75, 95, 112, 204). Moreover, the generation of reactive nitrogen species under such circumstances can further contribute to a higher intracellular redox state in which mitochondrial-derived nitric oxide is an important role player due to its interaction with superoxide to produce peroxynitrite, a potent reactive nitrogen species (75, 113, 204, 214, 281, 283). This is highly relevant within the context of hyperglycemia and CVD onset, wherein in vivo and in vitro studies demonstrate that peroxynitrite is an important causative agent in diabetes-mediated cardiovascular injury (44, 52). In addition, the protonation of peroxynitrite yields peroxynitrous acid, which is able to mediate oxidative/nitration reactions and can also decompose to form damaging hydroxyl radicals (49–51). These studies together show that increased production of both ROS and reactive nitrogen species plays a crucial role in the development of hyperglycemia-mediated CVD. However, defects in the antioxidant status can also contribute to higher ROS generation because oxidative stress

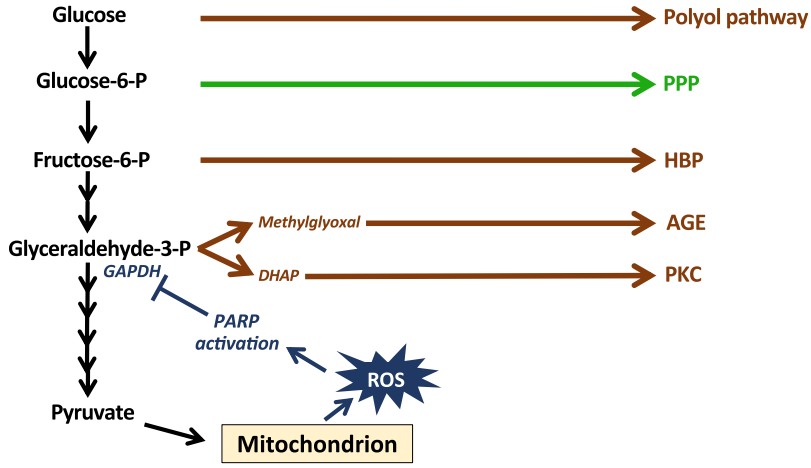

Fig. 1. The classic "unifying hypothesis" resulting in activation of the nonoxidative glucose pathways (NOGPs) with hyperglycemia. The proposal is made that higher glucose levels increase generation of mitochondrial reactive oxygen species (ROS). As a result, there is activation of poly(ADP-ribose) polymerase (PARP) to counter hyperglycemia-mediated DNA damage. However, the glycolytic enzyme GAPDH is poly(ADP-ribosyl)ated as a covalent post-translational modification, thereby resulting in a lowering of its activity. Subsequently, upstream glycolytic intermediates accumulate and are then shunted into the various NOGPs as indicated. Activation of the polyol pathway, the hexosamine biosynthetic pathway (HBP), advanced glycation end products (AGEs), and protein kinase C (PKC) triggers detrimental, downstream effects on the heart as discussed in this review. Conversely, higher flux through the pentose phosphate pathway (PPP) can attenuate cardiometabolic complications (102). DHAP, dihydroxyacetone phosphate.

occurs when the rate of prooxidant production exceeds intracellular antioxidant scavenging abilities (29, 156, 159).

It therefore remains unresolved whether higher ROS/reactive nitrogen species generation or diminished antioxidant surveillance or both are the major culprit under hyperglycemic conditions. In addition, other pertinent issues relating to the unifying hypothesis include *1*) mitochondrial superoxide being a poor candidate for transfer to the nucleus due to its relative instability and membrane impermeability, *2*) the relatively large amounts of peroxynitrite that would be required to survive transport to the nucleus to exert its detrimental effects, and *3*) the nature of GAPDH subcellular localization (mitochondrial vs. extramitochondrial) and its translocation to the nucleus (256). The precise mechanisms responsible for attenuated GAPDH activity with diabetes are also more complex than proposed. For example, higher levels of endogenous aldehydes found in individuals with diabetes can inhibit GAPDH (218). The higher NADH availability results in lowered GAPDH activity (202), whereas elevated NADH/NAD^+ levels also enhance GAPDH degradation (161). Diminished pyruvate dehydrogenase activity in the heart under diabetic conditions (55) could also lead to the upstream accumulation of glycolytic intermediates and thus potentially fuel NOGP activation under such circumstances. Further studies are therefore required to investigate these interesting possibilities to assess the validity of the unifying theory, especially within the clinical context. The various NOGPs will next be discussed and how their activation with hyperglycemia is linked to increased oxidative stress and the onset of cardiovascular complications.

Polyol pathway. Under normoglycemic conditions the glycolytic enzyme hexokinase phosphorylates most intracellular glucose into glucose-6-phosphate, whereas only relatively small amounts (~3%) enter the polyol pathway. However, under hyperglycemic conditions hexokinase becomes saturated, and the polyol pathway can sometimes account for more than 30% of overall glucose metabolism (84, 109, 294). In these conditions, the rate-limiting step is the reduction of glucose to sorbitol, which is catalyzed by aldose reductase, a member of the aldo-keto reductase family (246). Aldose reductase is a monomeric oxidoreductase that catalyzes the NADPH-dependent reduction of glucose and several endogenous aldehydes (37, 96, 105). For example, the aldehyde methylglyoxal is one of the best substrates for aldose reductase with a much higher affinity compared with glucose (301a). Sorbitol is subsequently converted to fructose by sorbitol dehydrogenase with NAD^+ required as a cofactor (37, 185, 246, 327) (Fig. 2).

The polyol pathway was first identified in 1956 (124), and aldose reductase has since been isolated and identified from several human and animal tissues, including the eye (118, 301f, 267), ovary (144), kidney (67), heart (301b, 268), and brain (68). Variable levels of aldose reductase expression are found in different tissues, and this may have an effect on the role of the polyol pathway in terms of pathophysiological outcomes (189). For example, relatively low levels of aldose reductase mRNA expression are found in the normal rat heart, although they are still severalfold higher than levels of sorbitol dehydrogenase (189). Aldose reductase gene expression and enzyme activity are regulated in a number of ways. For example, the epidermal growth factor-extracellular signal-regulated protein kinase can increase aldose reductase gene expression in

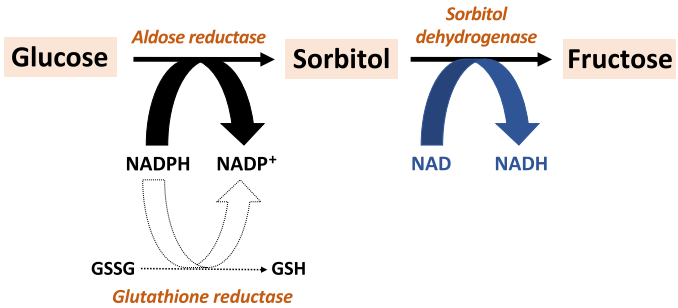

Fig. 2. Role of the polyol pathway in hyperglycemia-induced oxidative stress. Elevated glucose levels stimulate flux through the polyol pathway to generate sorbitol and fructose, respectively. The conversion of glucose to sorbitol by aldose reductase consumes NADPH, whereas the reaction catalyzed by sorbitol dehydrogenase generates NADH levels. The conversion of glucose to sorbitol by aldose reductase consumes NADPH, thus lowering its availability for the reaction in which oxidized glutathione (GSSG) is reduced to glutathione (GSH). As a result, antioxidant capacity is diminished, thereby contributing to a higher intracellular redox status.

response to oxidative stress in vascular smooth muscle cells (215). At the enzyme activity level, aldose reductase is regulated by nitric oxide availability, and this occurs by *S*-glutathiolation of the protein (276). However, with hyperglycemia there is attenuated nitric oxide generation, thereby leading to the lowering of nitric oxide-mediated repression of aldose reductase activity (282).

Higher activation of the polyol pathway can induce oxidative stress through multiple mechanisms. The depletion of NADPH and the corresponding attenuation of glutathione reductase activity result in decreased intracellular glutathione (GSH) levels (185, 284) (Fig. 2). This in turn lowers nitric oxide synthesis and availability because NADPH is a cofactor for nitric oxide synthase, which produces nitric oxide from L-arginine (284). Lower nitric oxide availability increases the risk for vascular complications under hyperglycemic conditions. Studies also show that aldose reductase reduces a number of lipid peroxidation-derived aldehydes together with its GSH conjugates, thereby contributing to intracellular toxicity and tissue and DNA damage, leading to cell death (apoptosis, necrosis) (275). The conversion of sorbitol into fructose (an end product of the polyol pathway) also increases NADH levels that can be used by NADH oxidases to elevate superoxide production in the vasculature and heart (110, 216, 235). In addition, mitochondrial transhydrogenase (located within the inner mitochondrial membrane) mediates the coupling of proton translocation across mitochondrial membranes to the transfer of reducing equivalents between NADH and NADPH (332). NADPH can thus be regenerated in this way although more studies are required to assess this pathway within the mammalian heart (332). Fructose can be further metabolized into fructose-3-phosphate and 3-deoxyglucosone, both more potent nonenzymatic glycation agents than glucose (114). In addition, the p38 kinase pathway is implicated in methylglyoxal-mediated upregulation of aldose reductase expression (326). Methylglyoxal exposure also elevated aldose reductase mRNA levels in a dose- and time-dependent fashion in rat aortic smooth muscle cells (54), whereas other researchers (326) have found that it resulted in a corresponding increase in aldose reductase protein levels and enzyme activity. This implies that enhanced flux through the polyol pathway increases AGE formation, thus further fueling ROS generation.

We propose that the damaging outcomes of higher polyol pathway activation occur within the vasculature and also by direct effects on the heart. For example, the polyol pathway is implicated in the pathogenesis of atherosclerosis; studies have shown that increased expression of human aldose reductase in transgenic mice results in accelerated atherosclerosis (302). Long-term polyol pathway activation also increased intimal thickening in dog coronary arteries, an effect that could be blunted by aldose reductase inhibition (153). In agreement, others found that oxidized LDL-induced upregulation of aldose reductase gene expression in human macrophages is proinflammatory (106). This effect was further amplified by hyperglycemia and therefore suggests a synergistic interaction with hyperlipidemia. Abnormal vascular smooth muscle cell proliferation may be a crucial mediator in this process because treatment with an aldose reductase inhibitor has been shown to prevent hyperglycemia-induced cell proliferation (280). Furthermore, in vitro polyol pathway inhibition promotes vascular endothelial cell migration, proliferation, and angiogenesis (80a) while limiting tumor necrosis factor-α-induced expression of adhesion molecules (239). Polyol pathway activation also triggered abnormalities in endothelium-dependent relaxation in aortas from streptozotocin-diabetic rats (47) and decreased nitric oxide release and functionality (46). Moreover, aldose reductase inhibition prevented the depression of endothelium-dependent aortic relaxations induced by diabetes (221). Increased activation of the polyol pathway also results in microvascular dysfunction with diabetes (129, 292), and this is likely due to higher levels of ROS and reactive nitrogen species and lowered nitric oxide availability. The experimental data together strongly support a role for the polyol pathway in the onset of atherosclerosis and heart failure (268), although at present there is limited evidence from clinical studies to support this.

What about in the context of ischemia-reperfusion? Polyol pathway activation increases severalfold during ischemia-reperfusion and is further upregulated under hyperglycemic conditions (149, 192, 281). Such activation can mediate ischemia-reperfusion injury in several ways. For example, polyol pathway activation results in opening of the mitochondrial permeability transition pore (7, 135, 136) and causes cardiac contractile dysfunction by increasing tyrosine nitration of the sarco(endo)plasmic reticulum Ca^{2+}-ATPase and the oxidation of ryanodine intracellular calcium channels, thus impairing its functional roles in terms of cardiac contractility (149, 281). In support of this, other researchers have implicated higher polyol pathway activation in calcium handling defects (65), whereas aldose reductase inhibition has been shown to lower intracellular calcium and sodium levels and to upregulate Na^+,K^+-ATPase activity in ischemic diabetic hearts (240). Polyol pathway inhibition also resulted in cardioprotection and decreased sorbitol and NADH/NAD^+ levels in diabetic hearts subjected to ischemia-reperfusion (241). Perturbed polyol pathway regulation is also linked to changes in glycolysis and ATP generation. For example, increased polyol pathway activation in diabetic hearts was associated with lower glycolysis and ATP generation. However, inhibition of aldose reductase enhanced glycolysis because of greater availability of NAD^+, a cofactor for GAPDH (295). Such inhibition also improved cardiac ATP generation and ionic homeostasis (241). These findings are further supported by another study in which sorbitol dehydrogenase inhibition increased glucose oxidation during myocardial ischemia-reperfusion, which resulted in lower cytosolic NADH/NAD^+ and higher ATP levels (134).

Aldose reductase inhibitors such as hydantoins (sorbinil) and carboxylic acids (tolrestat, penalrestat, epalrestat, and zopolrestat) were employed in experimental and clinical settings to counteract abnormal polyol pathway activation (66, 115, 141, 142, 284, 349). This approach has been successfully employed in experimental studies (e.g., aldose reductase inhibition decreased infarct size in an in vivo diabetic rat model of acute ischemia and reperfusion), and this likely due to combined antioxidant and anti-inflammatory effects (9). Polyol pathway inhibition also improved cardiac energy metabolism under normoglycemic and hyperglycemic conditions (241, 242), attenuated oxidative stress, and restored electrolyte homeostasis (219, 281, 293, 317). Moreover, data from our laboratory revealed that benfotiamine (a vitamin B_1 analog) treatment lowered polyol pathway activation and restored cardiac contractile function following ischemia-reperfusion under hyperglycemic conditions (192). However, the translation of experimental studies is lagging because some synthetic aldose reductase drugs have elicited deleterious side effects in clinical trials without showing significant beneficial effects (32). Interestingly, atorvastatin treatment of human umbilical vein endothelial cells diminished aldose reductase expression (252) and therefore offers a potentially novel way to blunt the damaging effects of higher polyol pathway activation under hyperglycemic conditions. Further in vivo and clinical studies are required to investigate this possibility. Decreased aldose reductase activity also prevents the production of sorbitol and downstream effects such as AGE formation and PKC activation, thereby showing that significant cross talk exists between the various NOGPs (147, 192). Together, these data demonstrate that the polyol pathway and especially aldose reductase are important targets for therapeutic interventions to potentially treat hyperglycemia-related CVD onset.

Advanced glycation end products. Nonenzymatic protein glycation occurs through a series of reactions that can be divided into *1*) stressors or sources of carbonyl agents that drive the reaction, *2*) propagators or reactive dicarbonyl agents that arise from precursor stressors, and *3*) end products that result in AGE formation because of the Maillard reaction (206). The protein glycation process starts with a nucleophilic addition between free ε-amino or NH_2-terminal groups of proteins and the carbonyl group of reducing sugars (normally glucose or glyceraldehyde) to form a reversible Schiff base (3, 4) (Fig. 3). The latter can rearrange into a stable, irreversible ketoamine or Amadori product (299, 311). The Schiff base is highly prone to oxidation and free radical generation leading to formation of the oxoaldehydes glyoxal and methyglyoxal in the so-called Namiki pathway of the Maillard reaction (208) that occurs early in the glycation process (Fig. 3).

The metal-catalyzed autooxidation of reducing sugars may also be involved in AGE formation (132, 318) because fructose-lysine can bind to redox-active copper to produce *N*-carboxy-methyl(lysine). Hydrogen peroxide is produced in the process, thereby contributing to the generation of AGE-mediated oxidative stress (255). This is an example of the Fenton reaction in which copper ions attached to glycated proteins become reactive or increase the reactivity of glycated proteins (10). AGEs can be generated from Amadori products by

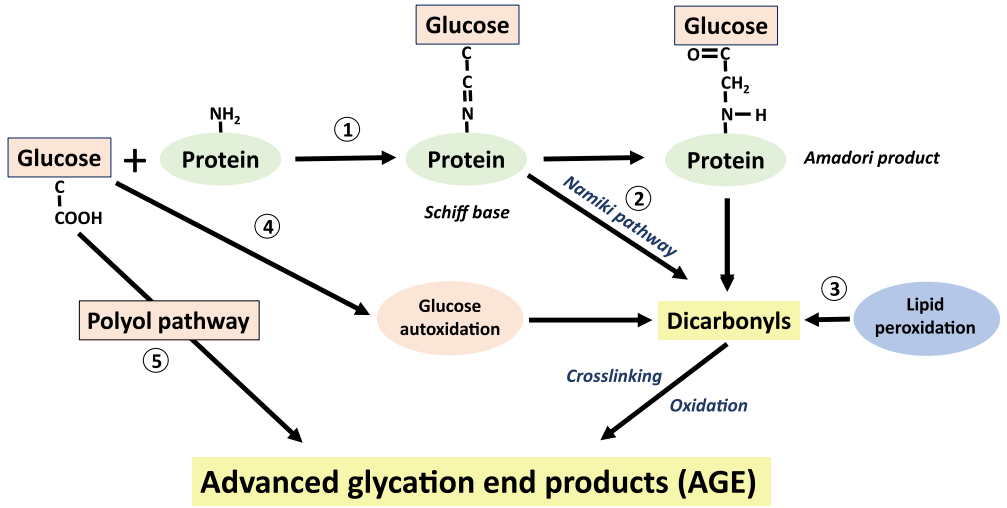

Fig. 3. AGE formation under hyperglycemic conditions. There a several ways by which AGEs can be generated under hyperglycemic conditions. *1*) The nonenzymatic attachment of glucose to free amino groups of target proteins results in the formation of an unstable Schiff base. This can undergo further isomerization to generate more stable Amadori products that can undergo dehydration and rearrangement to produce highly reactive dicarbonyls (or AGE precursors) such as methylglyoxyl, glyoxyl, and 3-deoxyglucosone. With additional oxidation and cross-linking to proteins, more stable and irreversible AGEs are formed. *2*) The Schiff base can undergo oxidative fragmentation to yield dicarbonyls by the so-called Namiki pathway. *3*) Lipid peroxidation, induced by oxidative stress, generates dicarbonyls. *4*) Glucose autoxidation (due to increased oxidative stress) can also produce dicarbonyls. *5*) With the polyol pathway, fructose can be converted to fructose-6-phosphate. Subsequently, fructose-6-phosphate can be converted to fructose-1,6-*bis*-phosphate. The latter can be then be further metabolized to generate glyceraldehyde-3-phosphate and methylglyoxyl.

auto-oxidation into reactive dicarbonyl products such as glucosones (e.g., methyglyoxal and 1,4-deoxyglucosone) (40). AGEs can also be altered by glycoxidation to produce *N*-carboxy-methyl(lysine) or pentosidine from lipids, also called advanced lipoxidation end products (Fig. 3).

Because methyglyoxal [a major source of intracellular AGEs (152)] is relatively cytotoxic, intracellular surveillance systems exist to ensure it can be metabolized after its formation. In this process methylglyoxal and its two-carbon analog glyoxal are metabolized to D-lactate by the cytosolic GSH-dependent glyoxalase 1 and 2 (288). However, dysregulation of such reactions is linked with pathophysiology, because attenuated glyoxalase-1 expression can occur with diabetes (244), leading to increased generation of intracellular AGEs (2, 200). Methyglyoxal can also promote oxidative stress by causing glycation and inactivation of glutathione reductase and peroxidase (200), whereas its accumulation directly depletes GSH in various cell types (196, 320). Because GSH is a cofactor for the glyoxalase system, lower availability will impair methyglyoxal degradation and establish a vicious cycle that will further elevate intracellular methyglyoxal levels and downstream effects (288). Such detrimental outcomes are well known to be accelerated with diabetes (254, 285, 334).

Increased serum AGE levels can predict total and CVD mortality in women with diabetes and those without diabetes (157), although it is also an independent prognostic factor for heart failure (166). Elevated *N*-carboxy-methyl(lysine) serum levels are also associated with the onset of ischemic heart disease in persons with type 2 diabetes (1), whereas it puts older adults at higher risk of all-cause and CVD mortality (259). Because soluble receptors for AGEs (sRAGE) act as a decoy receptor for AGEs and thus reflect cell surface AGE receptor (RAGE) activity, it can be exploited as a biomarker for cardiovascular complications triggered by AGE-RAGE activation (6a). For example, serum sRAGE levels are independently correlated with a marker of central aortic stiffness, therefore suggesting a potential role for RAGE in this process (260, 335). Other researchers have found that sRAGE is a predictor of aortic valve calcification (346) and correlates with dysfunctional aortic microstructure (33). It is also an inverse marker of left ventricular hypertrophy in patients with chronic kidney disease, therefore indicating that the RAGE pathway may be a causal risk factor for cardiac hypertrophy in this instance (174). In addition, plasma levels of sRAGE and *N*-carboxy-methyl(lysine) are increased with chronic heart failure (30), whereas AGE concentration is an independent marker of postinfarction heart failure development risk (245). sRAGE levels may also be useful for risk stratification in patients with heart failure (166). However, a recent multivariate analysis indicates that the ratio of AGEs to sRAGE may be a better predictor of flow-mediated dilatation compared with the separate analysis of such parameters (150). These findings also show that sRAGE may counteract the damaging effects of the AGE-RAGE axis on the vasculature (150).

Several laboratory and clinical studies have demonstrated an association between AGE levels and atherosclerosis development (278) with and without diabetes (99, 121, 297, 301d). For example, AGEs have been identified in endothelial cells of normal and atherosclerotic vessel walls in human carotid arteries (187), whereas higher AGE and sRAGE levels are associated with incident coronary heart disease manifesting with type 2 diabetes (12, 61). Serum AGE concentrations may also reflect the severity of coronary arteriosclerosis in this instance (160). Furthermore, carotid intima-media thickness is positively correlated with oxidized and AGE-modified LDL (133), whereas skin autofluorescence (an indicator of AGE levels) is increased with subclinical and clinical atherosclerosis (independent of diabetes) (73). AGE-induced modification of circulating proteins may contribute to such described effects. For example, AGE content of apolipoprotein B100 (of LDL)

and oxidative damage in patients with type 2 diabetes were higher compared with healthy subjects (233). AGE-modified LDL can trigger detrimental outcomes by induction of proinflammatory cytokine production in human coronary artery endothelial cells and macrophages (127). In this process, AGE-LDL-mediated effects occur via a Toll-like receptor-4-mediated signaling pathway. The AGE-RAGE axis also promotes an inflammatory environment by increasing TNF-α and IL-6 together with enhanced endothelin and decreased nitric oxide levels [reviewed in Piarulli et al. (228)]. Furthermore, AGE-modified BSA and methylglyoxal exposure caused apoptosis of neutrophils and expression of the β_2-integrin subunit Mac-1 (CD11b), resulting in increased formation of platelet-neutrophil aggregates (103). Methylglyoxal-arginine-derived AGE was also associated with plasma-soluble vascular cell adhesion molecule-1 in individuals with diabetes with this likely reflecting endothelial dysfunction (301c). In addition, AGE-mediated modification of apolipoprotein A-I (the principal protein component of HDL) impaired its cardioprotective and antiatherogenic properties, including the ability to promote cholesterol efflux and inhibit the expression of adhesion molecules (126).

Animal studies provide additional support for such findings, further emphasizing a crucial role for AGEs in the development of atherosclerosis. For example, hyperglycemia-induced impairment of endothelium-dependent vasorelaxation in rat mesenteric arteries is mediated by higher methylglyoxal levels in an ROS-dependent manner (35). Increased methylglyoxal levels and subsequent RAGE activation also increased vascular adhesion in mice and augmented atherogenesis (289). Moreover, a mouse model of diabetes and atherosclerosis lacking RAGE displayed significantly less aortic plaque area (312). Our laboratory and others also found increased AGE levels following ischemia and reperfusion in the absence of atherosclerosis (39, 184, 192, 296), demonstrating more direct effects on rodent hearts. Such detrimental effects of elevated AGEs on cardiac contractile dysfunction are also much more pronounced under hyperglycemic conditions following ischemia-reperfusion (184, 192). Together, these studies establish a robust link between the AGE-RAGE pathway and the onset of CVD under hyperglycemic conditions.

What are the underlying mechanisms whereby AGEs can mediate such detrimental effects? The damaging consequences of AGEs can occur through increased glucose uptake by target cells or by modification of circulating proteins and/or interactions with RAGE (210, 331). AGEs can form cross-links with target proteins (e.g., serum albumin, LDL, HDL, collagen, and numerous intracellular proteins), thereby changing their structure and function (72, 254, 334). For example, glycation-derived modification of aortic collagen (53) increases matrix stiffness, making it resistant to hydrolytic turnover, resulting in an accumulation of extracellular matrix proteins [reviewed in Zhao (345)]. Typical downstream effects of AGEs on proteins include altered enzyme activity, decreased ligand binding, modification of protein half-lives (307), and glycation-derived free radicals that lead to protein fragmentation and oxidation of nucleic acids and lipids (16, 17). AGEs can promote heart failure via the maturation of dendritic cells, and coculturing of such cells with cardiomyocytes has resulted in upregulation of hypertrophy-associated genes (48). Transcriptional regulatory mechanisms likely include ROS production through a PKC-mediated Nox2 pathway that results in nuclear factor-κB (NF-κB) activation and upregulation of atrial natriuretic factor mRNA in cardiomyocytes (340). AGE cross-linking also plays a role in mediating diastolic compliance in volume-overload hypertrophy (123). Its upregulation in cardiac fibroblasts also resulted in stimulation of signaling cascades (p38 kinase and extracellular-related signal kinases) together with metalloproteinases activation that may be responsible for tissue remodeling and the onset of fibrosis (71). In support of this, AGE inhibition was shown to prevent diabetes-induced atrial fibrosis (154).

RAGEs are widely distributed in macrophages, endothelial cells, cardiomyocytes, and mesangial cells (34, 334), and the elucidation of its modulatory role or roles and downstream signal transduction pathways are areas of intensive investigation. The AGE-RAGE axis may directly affect myocardial calcium homeostasis because RAGE overexpression has resulted in the lowering of systolic and diastolic intracellular calcium concentrations (226). Moreover, AGEs also form on sarco(endo)plasmic reticulum Ca^{2+}-ATPase and the intracellular ryanodine receptor 2 during diabetes (23, 24) and can cause partial depletion of sarcoplasmic reticulum calcium (329). High AGE availability can also lead to impaired Na^+/K^+-ATPase activity in cardiomyocytes (336).

Previous studies have shown that RAGE binding initiates PKC activation (199, 258), tyrosine phosphorylation of Janus kinase/signal transducers and activators of transcription (131), leads to recruitment of phosphatadiylinositol-3 kinase to the Ras-dependent mitogen-activated protein kinase (178) or PKC (74, 164, 171), and induces oxidative stress cascades that can culminate in NF-κB and activator protein-1 transcriptional activation (25, 334, 350). Moreover, nitric oxide signaling is a crucial pathway that is impaired during this process (350) and can eventually lead to the development of atherosclerosis and CVD under hyperglycemic conditions. Initiation of such signaling pathways can also lead to a tissue-specific proinflammatory environment, whereas RAGE activation stimulates the renin-angiotensin system leading to increased angiotensin II formation (87, 97, 201). In support of this concept, blockade of the renin-angiotensin system activation led to decreased AGE levels, thereby preventing detrimental microvascular effects such as retinopathy (87, 97, 201).

The AGE-RAGE axis also elicits detrimental effects on mitochondrial function. For example, methylglyoxal-induced dysfunction of cardiomyocytes was associated with mitochondrial membrane depolarization and reduced glycogen synthase kinase-3β inactivation (188), whereas RAGE signaling decreased cardiomyocyte mitochondrial respiration (211). AGEs also perturb organization of desmin filaments that normally support stress response and mitochondrial function in cardiomyocytes (80). The AGE pathway can also lead to impaired function of thioredoxin (which usually possesses cytoprotective functions such as antiapoptotic and antioxidant functions) because methylglyoxal exposure was shown to result in thioredoxin posttranslational modification and increased hypoxia-reoxygenation injury in cardiomyoblasts (310). Other researchers have found that RAGE modulates myocardial ischemia-reperfusion injury via nitration and inactivation of thioredoxin (184). Collectively, these findings demonstrate that the effects of AGE-RAGE cover a range of cardiac cell types and that it also triggers several damaging signaling pathways that can contribute to CVD onset and progression.

Inhibition of the AGE pathway opens exciting possibilities for the prevention of CVD in individuals with diabetes, and various strategies have been developed to limit AGE-associated detrimental effects. These include the trapping of reactive dicarbonyl species, use of antioxidants such as transition-chelating metal ions and free radical scavengers, employment of agents that break AGE cross-links, blunting RAGE and its downstream signaling pathways, enhancing glycemic control, and inhibiting aldose reductase and shunting flux into the pentose phosphate pathway by transketolase activation (227). For example, pimagedine (also known as aminoguanidine) prevents the formation of irreversible AGEs by trapping reactive dicarbonyl intermediates (36, 286, 287). This approach has yielded positive outcomes such as slowing the progression of overt nephropathy, retinopathy, and atherosclerosis. However, it did not significantly lower serum creatinine and urine albumin in type 1 diabetes, possibly because of increased renal clearance (28). Aminoguanidine treatment also resulted in antifibrotic and antihypertrophic effects in rats that can be mainly attributed to its ROS quenching efficacy and direct interaction with metalloproteinases (225). Data generated by our group also demonstrated that treatment of ex vivo rat hearts with aminoguanidine during reperfusion attenuated myocardial AGE levels and improved cardiac contractile function under hyperglycemic conditions (192). This was associated with decreased oxidative stress and cell death (192). Furthermore, others (217) found that the reduced ventricular compliance that occurs with diabetes as a result of myocardium stiffness was prevented by aminoguanidine together with improved rat heart function and a reduction in collagen AGE formation (217).

The use of alagebrium chloride (ALT-711), which breaks preaccumulated AGEs, showed beneficial effects in preventing diabetic cardiomyopathy (11) because its use resulted in decreased left ventricular mass, improved left ventricular filling, and quality of life in patients with diastolic heart failure (179, 180). Preclinical research showed that alagebrium chloride (ALT-711) partially normalized sarcoplasmic reticulum calcium handling and improved diabetic cardiomyopathy (167), further supporting its use. sRAGE can also be employed as a therapeutic strategy to prevent interaction of AGEs with RAGE and limit damaging downstream effects. For example, intracoronary sRAGE administration attenuated myocardial fibrosis and ischemia-reperfusion injury through a transforming growth factor-β_1-dependent mechanism (186). The employment of a RAGE antibody prevented left ventricular diastolic chamber stiffness, and its use led to lower collagen expression and a switch in expression of myosin from the fetal to the adult isoform (213).

Glycemic control is another CVD preventive measure to consider in view of the fact that AGE formation is greatly accelerated under high glucose conditions (205), whereas lower glucose levels decrease activation of the first step in the Maillard reaction. There is limited information on the effect of antidiabetic drugs on AGE formation and downstream effects within the clinical setting. However, animal studies have demonstrated that metformin use led to a decrease in collagen glycation levels and heart vessel stiffness together with maintained cardiac function (20, 148), whereas its use led to decreased hyperglycemia-induced cardiomyocyte injury by inhibiting RAGE expression (343). Moreover, thiazolidinediones (195) and aspirin formulations have been successfully used to diminish AGE levels (301, 330). In experiments of their use, the peroxisome proliferator-activated receptor-γ activator pioglitazone improved heart function by decreasing AGE expression in diabetic rats subjected to myocardial infarction (195). In addition, pioglitazone alleviated AGE-induced maturation of dendritic cells and resulted in improved heart function (48). Rosiglitazone therapy also resulted in reduced cardiac fibrosis and improved left ventricular diastolic function together with suppression of RAGE and connective tissue growth factor expression in the diabetic myocardium (195). These findings therefore support the potential use of proliferator-activated receptor-γ agonists as antifibrotic agents in individuals with diabetes (137).

Rosuvastatin, a 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor, attenuated plaque area in diabetic and atherosclerotic mice in the absence of lipid-lowering effects (45). This was associated with lower AGE and RAGE levels in plaques (45). In support of those findings, other researchers found that simvastatin use inhibited plaque RAGE expression by decreasing myeloperoxidase-dependent AGE generation in human atherosclerotic plaques (69). In addition, use of the antihypertensive drug losartan resulted in decreased vascular AGE levels and suppressed RAGE and NF-κB activation to enhance antioxidant capacity and thereby improve endothelial function (348). Additional therapeutic approaches include administration of vitamins and derivatives that also exhibit the potent ability to lower AGEs in animals (152, 192) and persons (230) with diabetes. Moreover, cardiac fibrosis and AGE accumulation were attenuated in exercised rats (319). Novel therapeutic interventions under development include small interfering RNA (siRNA) techniques (e.g., use of siRAGE resulted in reduced apoptosis and inflammatory cytokine release and subsequently led to attenuation of left ventricular remodeling in a rat myocardial infarction model). This approach emerges as an exciting strategy for treating myocardial infarction because its use has resulted in negligible toxicity and enhanced intracellular delivery efficiency (128).

From these studies, it emerges that hyperglycemia-mediated AGE stimulation and/or AGE-RAGE activation play a central role in the pathogenesis of cardiometabolic complications and therefore constitute a major therapeutic target. However, additional factors are also likely to play a role because the Diabetes Control and Complications Trial showed that CVD complications occur in association with increased levels of AGEs despite the presence of adequate glycemic control (77, 205). This observation is consistent with the hypothesis that other drivers such as oxidative stress also contribute to the production and accumulation of AGEs (13, 17) and that metabolic memory predisposes persons with and without diabetes to CVDs even after glycemic control (116). However, further clinical studies are required to evaluate the efficacy of AGE reduction and/or preventing its interaction with RAGE.

Protein kinase C. PKC is a serine/threonine-related family of protein kinases that controls numerous intracellular signal transduction pathways (212). Twelve PKC isoforms have thus far been identified that differ in terms of structure and substrate requirements [reviewed in Geraldes and King (104)]. Several isoforms, including PKC-α, -β_1, -β_2, -γ, -δ, -ε, -θ, and -η are activated by the second-messenger diacylglycerol (DAG), an important signaling molecule that regulates vascular functions such as permeability, growth factor signaling, vasodilator re-

lease, and endothelial activation (5, 37, 155, 261). DAG is formed by multiple pathways that include agonist-induced hydrolysis of phosphatidylinositol by phospholipase-C (5, 71a) or de novo synthesis from dihydroxyacetone phosphate and glycerol-3-phosphate (322). However, other researchers have established that the phospholipase-C pathway does not contribute to elevated DAG levels (i.e., exposure of rat aortic smooth muscle cells to high glucose concentrations increased DAG levels without changing levels of inositol 1,4,5-trisphosphate, a derivative of phosphatidylinositol hydrolysis) (322). In a state of hyperglycemia, greater availability of glycolytic intermediates such as dihydroxyacetone can be converted to lysophosphatic acid and thereafter to phosphatidic acid. DAG kinase can subsequently convert phosphatidic acid to DAG and vice versa. Increased PKC levels with diabetes are found in several tissues including the retina (262), aorta, heart (140, 192), renal glomeruli (143), liver, and skeletal muscle (301e). Moreover, PKC activities and total DAG levels were significantly upregulated in the aorta and hearts of diabetic rats; in that study (140), hyperglycemia was a causal factor because a higher glucose supply resulted in increased DAG levels in aortic endothelial and smooth muscle cells. In the PKC activation process the molecule undergoes a series of complex phosphorylation steps during which it can translocate from the cytosol to the sarcolemma. PKC activation can be mediated through hyperglycemia-induced ROS including hydrogen peroxide and mitochondrial superoxide, thereby further exacerbating oxidative stress and leading to damaging downstream effects (71a, 155, 214, 304). As we discussed earlier in this review article, hyperglycemia-mediated activation of the NOGPs can also stimulate the PKC signaling pathway.

There is a growing body of evidence to show that higher PKC activation triggers hyperglycemia-induced cardiometabolic perturbations such as changes in blood flow, basement membrane thickening, extracellular matrix expansion, vascular permeability, angiogenesis, cell growth, and enzymatic activity alterations (71a, 140, 322, 323). PKC activation also directly enhances the permeability of macromolecules across endothelial or epithelial barriers by phosphorylating cytoskeletal proteins or indirectly by controlling expression of various growth modulators such as VEGF (5, 37, 155, 304). The effects of PKC activation on nitric oxide are unclear, although there is evidence that it can lower nitric oxide production and thereby contribute to endothelial dysfunction (37, 155, 304). PKC-generated prooxidants promote formation of oxidized-LDL (270) that can cause endothelial cell activation and injury, crucial steps in the pathogenesis of atherosclerosis. In this process, lysophosphatidylcholine, a major constituent of oxidized-LDL, further increases activation of PKC and subsequent ROS formation (328). The downstream target of PKC activation is NADPH oxidase (321), which is regulated by various oxidase subunits.

Nox2 and Nox4 are robustly expressed in various heart cell types, including cardiomyocytes, endothelial cells, vascular smooth muscle cells, and cardiac fibroblasts [reviewed in Akki et al. (6) and Dworakowski et al. (86)]. Nox4 is constitutively active, whereas Nox2-containing NADPH oxidase requires activation of various cytosolic oxidase subunits such as $p67^{phox}$ binding to the active site on Nox2. The interaction of $p47^{phox}$ with $P22^{phox}$ is required to facilitate this process, whereas binding of the small GTP-binding protein Rac1 is needed for full activation [reviewed in Akki et al. (6) and Dworakowski et al. (86)]. NADPH oxidase activity can be further elevated by higher endothelin-1 levels and is associated with enhanced angiotensin II stimulation in endothelial cells, which leads to $p47^{phox}$ phosphorylation (14, 176). Quagliaro et al. (231) also demonstrated that endothelial cells exposed to an intermittent high glucose challenge resulted in NADPH oxidase activation that was sensitive to PKC inhibitors. Furthermore, A-kinase anchoring protein-150 (a scaffold protein) is upregulated with hyperglycemia and promotes glucotoxic effects through the PKC-$p47^{phox}$-ROS pathway, which induces myocardial dysfunction, apoptosis, and oxidative stress (339). PKC exerts such effects because it is able to directly phosphorylate Nox subunits, thereby resulting in activation of NADPH oxidases. For example, an in vitro study found that the PKC-α isoform could bind directly to and phosphorylate Nox5 to increase ROS production in endothelial cells (58). Other researchers have also established that Nox2 is phosphorylated by PKC in human neutrophils to enhance catalytic activity and assembly of the NADPH oxidase complex (232). These data confirm that PKC is activated under hyperglycemic conditions and that this process can be regulated by several mechanisms such as increased DAG levels, phosphorylation, NOGP activation, and elevated ROS.

Previous studies have demonstrated that the PKC-α, -β, and -δ isoforms can elicit detrimental effects on the myocardium under hyperglycemic conditions and lead to contractile dysfunction (59, 111, 140, 183, 263, 269). For example, PKC-α promotes cardiac fibrosis and heart failure by stimulating galectin-3 expression, which is a small lectin-like protein that plays a significant role in the onset of heart failure (269). Moreover, increased ROS production regulated by PKC-δ is in part responsible for the induction of apoptosis in cardiomyocytes exposed to hyperglycemic conditions (263). The PKC-β_2 isoform is most frequently implicated in diabetic cardiovascular complications (173, 324) and is preferentially overexpressed in the myocardium of individuals and animals with diabetes (63, 264). PKC-β_2 can also result in a proinflammatory and proatherogenic environment in macrophages of diabetic mice, an effect that could be prevented by treatment with ruboxistaurin, a selective PKC-β_2 inhibitor (162). In support of this, depletion of the PKC-β gene or ruboxistaurin treatment decreased atherosclerosis in mice by inhibiting the early growth response protein that regulates vascular cell adhesion molecule-1 expression and metalloproteinase-2 activity (119). PKC-β_2 activation can also affect nitric oxide regulation and production [e.g., it has suppressed nitric oxide regulation and formation in endothelial cells (26, 27)]. PKC-β_2 activation can interfere with eNOS localization to caveolin-3 in cardiomyocytes to impair nitric oxide release (94), and excessive PKC-β_2 activation is associated with diminished caveolin-3 expression (173). This in turn contributes to abnormal Akt/eNOS signaling under hyperglycemic conditions (173).

Cardiac-specific overexpression of PKC-β_2 has resulted in ventricular hypertrophy, cardiomyocyte necrosis, multifocal fibrosis, and decreased left ventricular performance without vascular lesions (308). Other researchers have established that PKC-β_2-induced myocardial hypertrophy could be prevented by antioxidant treatment, thereby implicating oxidative stress in this process (324). Moreover, in our laboratory we found enhanced PKC activity and increased PKC-β_2 protein expres-

sion in hearts subjected to ischemia-reperfusion under hyperglycemic conditions (192). PKC inhibition under such conditions resulted in cardioprotection, thus emphasizing the detrimental role of PKC activation under such circumstances. To support this finding, increased cardiac PKC activity was found during ischemia-reperfusion and hyperglycemia (277). PKC activation during ischemia-reperfusion may, however, be either cardioprotective or -damaging depending on which isoform is activated and the timing of activation in the protocol (i.e., preischemia, during ischemia, postischemia, and reperfusion). For example, various studies have highlighted the role of PKC-ε and -ζ in cardio-protection under normoglycemic (197, 325, 342) and hyperglycemic conditions (190) with or without ischemia and reperfusion.

What about the feasibility of using PKC as a therapeutic option for treating cardiometabolic diseases? It is an arduous task to target a specific isoform because the PKC family represents a broad spectrum, and some isoforms can also elicit cardioprotection. Thus the challenge is to develop isoform-specific PKC inhibitors that will be effective not only in cell- and animal-based studies but also within the clinical context, bearing in mind species-related differences in isoform expression. Ruboxistaurin is a selective PKC-β_2 inhibitor that was evaluated within the clinical setting; studies revealed that it prevented a decrease in visual acuity in individuals with diabetes and visual impairment (229) and also attenuated the loss of glomerular filtration rate and proteinuria in individuals with diabetes (298). However, only a few studies have evaluated whether ruboxistaurin offers benefits to patients suffering from cardiometabolic complications. In two separate clinical studies performed in patients with diabetes, ruboxistaurin treatment improved endothelium-dependent vasodilation (19, 198). However, additional and larger clinical studies are required to evaluate the efficacy of PKC inhibitors as a viable therapeutic option for cardiovascular complications.

The majority of studies targeting PKC have been completed by laboratory-based analyses. For example, PKC-α and -β inhibition restored cardioprotection that is usually mediated by ischemic preconditioning (265). Ruboxistaurin also improved cardiac function in diabetic animals (314) and ameliorated cardiac hypertrophy and dysfunction (314). It also attenuated cardiac microvascular ischemia-reperfusion injury in diabetic rats partly because of its maintenance of endothelial barrier function and antiapoptotic effects (138, 313). In addition, ruboxistaurin treatment blunted atherosclerosis in diabetic and atherosclerotic mice by limiting monocyte adhesion, macrophage infiltration, and atherosclerotic plaque formation (85).

These studies taken together show that PKC activation plays a pivotal role in CVD development with diabetes by eliciting both direct effects on the heart and/or by contributing to the onset of atherosclerosis. However, it remains unclear whether PKC inhibition is an effective therapeutic strategy for treating diabetes-related CVD because very limited clinical data have been generated thus far to make that determination.

Hexosamine biosynthetic pathway. The HBP involves the conversion of glucose to fructose-6-phosphate, and thereafter fructose-6-phosphate to glucosamine-6-phosphate by the rate-limiting enzyme glutamine:fructose-6-phosphate amidotransferase. Uridine diphosphate-*N*-acetylglucosamine (UDP-GlcNAc) is the major end product formed from glucosamine-6-phosphate, which together with other HBP-generated amino sugars, provides essential building blocks for glycosyl side-chains of proteins and lipids (43). UDP-GlcNAc is further processed by the second rate-limiting enzyme *O*-linked β-*N*-acetylglucosaminyl transferase, which transfers GlcNAc moieties to side-chain hydroxyls of serine and threonine residues, thereby generating *O*-linked glycosylated proteins (Fig. 4). The removal of *O*-GlcNAc residues is carried out by β-*N*-acetylglucosaminidase. Such modification of serine and threonine residues of nuclear and cytoplasmic proteins was first identified in 1984 (291) and is also targeted by the phosphorylation process, showing that *O*-GlcNAcylation and phosphorylation have some reciprocity (168, 194). The addition of *O*-GlcNAc residues onto proteins can exert several functional effects that include the regulation of protein phosphorylation and protein function; alteration of protein degradation, which contributes to the intracellular localization of proteins; and modulation of protein-protein interactions and mediation of gene transcription (337).

The HBP usually functions as a nutrient sensor under physiological conditions (117). However, with hyperglycemia, excess glucose can be shunted into this pathway resulting in detrimental effects such as the development of insulin resistance, renal and vascular complications, and increased damage with ischemia-reperfusion (43, 120, 147, 193, 333). At present, very few clinical studies exist to demonstrate a causal link

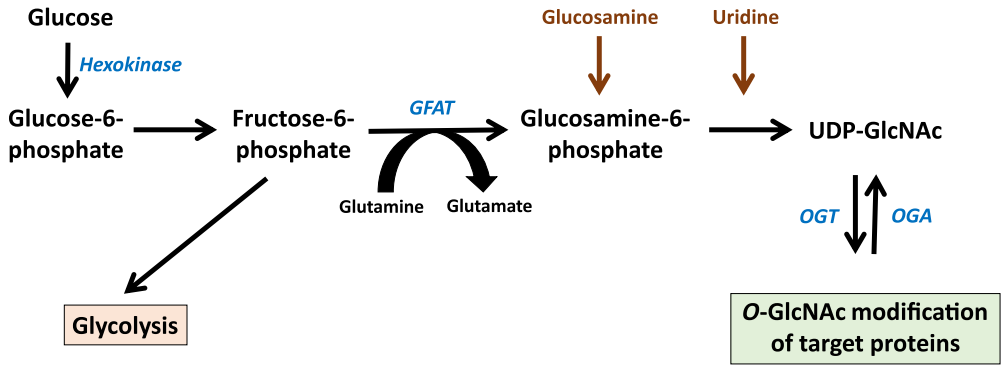

Fig. 4. The HBP results in posttranslational modification of target proteins. With hyperglycemia, the HBP diverts flux from glycolysis by the conversion of fructose-6-phosphate to glucosamine-6-phosphate, a reaction catalyzed by the rate-limiting enzyme glutamine fructose-6-phosphate amidotransferase (GFAT). The HBP culminates in the attachment/removal of *O*-linked *N*-acetylglucosamine (*O*-GlcNAc) moieties onto target proteins by *O*-linked β-*N*-acetylglucosaminyl transferase (OGT) and β-*N*-acetylglucosaminidase (OGA), respectively.

between HBP activation and high glucose-induced complications in diabetic individuals. Studies from our laboratory recently showed increased HBP activation and *O*-GlcNAc levels in leukocytes of individuals with diabetes and prediabetes (272) and decreased β-*N*-acetylglucosaminidase gene expression with type 2 diabetes (64). Moreover, other researchers have found that individuals with type 2 diabetes displayed an association of glutamine:fructose-6-phosphate amidotransferase mRNA levels and enzyme activity with postprandial hyperglycemia and oxidative stress (274). In those studies, HBP activation correlated with thiobarbituric acid reactive substances and protein carbonyl content, both markers of oxidative stress.

Investigations into the role of the HBP on cardiac function have generated contradictory findings over whether increased activation is beneficial (56, 57) or harmful (191, 236) within this context. Several studies have found that increased *O*-GlcNAcylation under hyperglycemic conditions elicits detrimental effects on cardiac contractile function (60, 130, 191). Because UDP-GlcNAc is a substrate for the glycosylation of important intracellular modulators (37) that include transcription factors, UDP-GlcNAc can affect the expression of several genes that regulate cardiovascular function. For example, HBP-mediated activation of plasminogen activator inhibitor-1 via specificity protein 1 (Sp1) can lead to the development of diabetes-induced vascular complications (100, 107, 108). Furthermore, studies performed in our laboratory have established that HBP activation induced the gene promoter of the cardiac isoform of acetyl-CoA carboxylase via the transcriptional modulator, upstream stimulatory factor 2 (139). We propose that such acetyl-CoA carboxylase-β induction may trigger serious downstream effects such as the inhibition of fatty acid β-oxidation, and the onset of myocardial insulin resistance and cardiovascular complications. Increased protein *O*-linked GlcNAcylation can also result in diminished expression of sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase in the diabetic heart thereby, leading to impaired myocardial contractility (60, 130). Furthermore, *O*-GlcNAcylation can result in lowered phospholamban phosphorylation that may contribute to decreased systolic function (98). HBP activation can also accelerate atherosclerosis (81, 92, 273) by decreasing eNOS levels in the vascular endothelium and thereby promoting endoplasmic reticulum stress, lipid accumulation, and increased inflammatory gene expression (31, 253, 316) that will predispose to acute myocardial infarction. Other researchers have found that a proatherogenic milieu can also be created by increased vascular wall thickening due to the accumulation of hyaluronan; synthesis of the latter occurs as a result of *O*-GlcNAcylation of hyaluronan synthase 2 (303).

Our laboratory has established that enhanced HBP activation under high glucose conditions, followed by ischemia and reperfusion elicits detrimental effects on cardiac contractile function together with increased oxidative stress and apoptosis (192). Moreover, these data revealed a novel pathway whereby increased HBP activation triggers cardiac apoptosis (236, 237). In this process, HBP activation resulted in greater Bcl-2-associated death promoter (BAD) *O*-GlcNAcylation and decreased BAD phosphorylation (Ser136) in hyperglycemic hearts. These data are in agreement with other results showing competition by phosphorylation and *O*-GlcNAcylation for the same or neighboring site(s) on target proteins. Moreover, we found increased BAD-Bcl-2 dimerization (proapoptotic) in hyperglycemic hearts, thus strongly implicating this pathway in diabetes-related onset of heart disease (Fig. 5) (236, 237). Inhibition of HBP provided cardioprotection (191, 192) and led to improved cardiac contractile function and decreased infarct size, apoptosis, and oxidative stress under hyperglycemic conditions following ischemia-reperfusion (191, 192). Taken together, these findings demonstrate that excessive HBP activation can exert harmful outcomes and contribute to cardiac dysfunction.

However, some studies have reported beneficial effects of increasing HBP activation on heart function (181, 182). The protective effects observed may be due to experimental protocol differences such as the streptozotocin-diabetic hearts employed being preconditioned, relatively low glucose levels (5 mM) employed for perfusion studies, and the duration of high glucose exposure. Nevertheless, the mechanisms that are likely involved in cardioprotection include decreased calcium influx into cardiomyocytes, thus preventing calcium overload associated with ischemia-reperfusion injury (182). In addition, an acute elevation of the HBP may trigger a prosurvival response that is associated with increased production of well-known cardioprotective regulators such as the heat shock proteins Hsp70 and Hsp40 (338). A similar trend was noted by others who found that higher HBP activation can exert both anti-inflammatory and prooxidative effects in endothelial cells under hyperglycemic conditions (238). It is likely that such differences stem from variations in experimental models, the nature of the stress condition (acute vs. chronic), the specific target proteins that are modified by *O*-GlcNAcylation, and other unknown factors. Of note, a recent study established that altered *O*-GlcNAcylation in the diabetic heart is due to subcellular redistribution of *O*-linked β-*N*-acetylglucosaminyl transferase and β-*N*-acetylglucosaminidase, an additional factor to consider in this context (243). Further studies are therefore required to gain greater insight into the underlying mechanisms and context responsible for such varying responses to *O*-GlcNAcylation of target proteins.

Interrelationship Between NOGPs

It is clear that hyperglycemia-induced intracellular and extracellular changes result in alterations of signal transduction pathways that can affect gene and protein function, thereby leading to cellular dysfunction and cardiac damage. These findings also indicate a unique interplay between the NOGPs and the downstream convergence of detrimental effects such as myocardial oxidative stress, further NOGP activation, apoptosis, and impaired contractile function. Thus we suggest that a vicious metabolic cycle is established whereby hyperglycemia-induced NOGP stimulation further fuels its own activation by generating even more oxidative stress and exacerbating damaging effects in the heart (Fig. 6). If flux therefore can be shunted away from the earliest pathway(s) activated in this scheme it should be possible to attenuate activation of the other NOGPs.

In agreement with this observation, higher pentose phosphate pathway (PPP) activation can attenuate cardiometabolic complications by shunting flux away from the damaging NOGPs (108). The PPP plays an essential role in cell

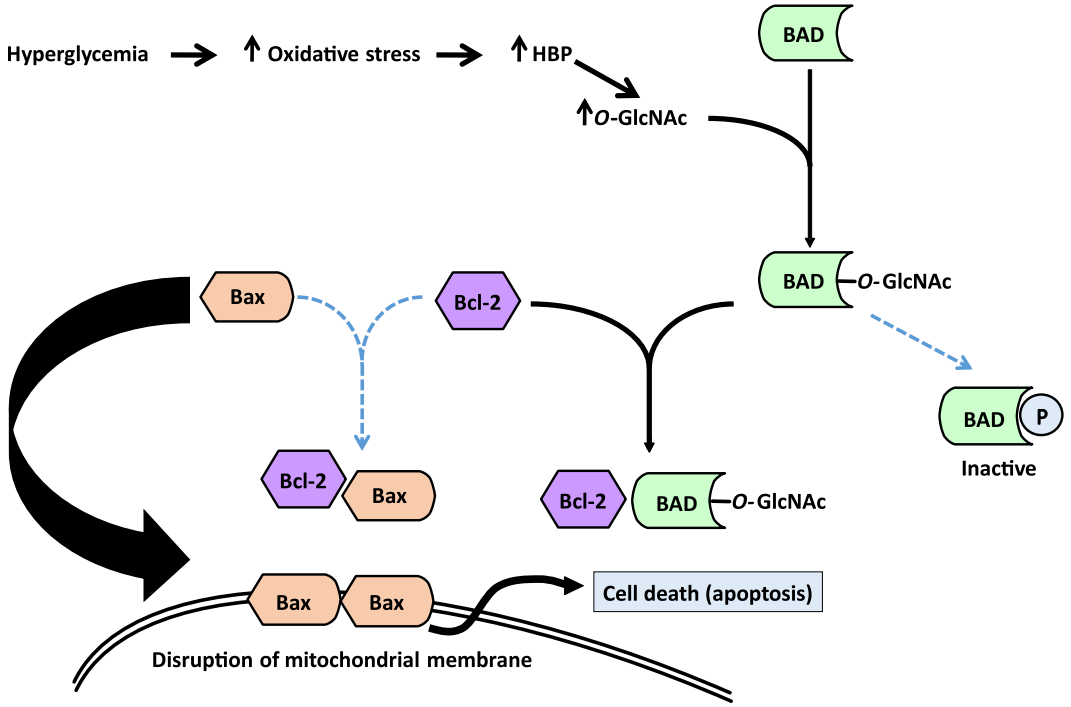

Fig. 5. Novel pathway by which increased HBP activation can trigger myocardial apoptosis. Hyperglycemia-mediated activation of the HBP leads to increased Bcl-2-associated death promoter (BAD) *O*-GlcNAcylation. In parallel, there is decreased BAD phosphorylation and hence less inactivation occurs. Subsequently, there is greater dimerization of *O*-GlcNAcylated BAD with Bcl-2, meaning less dimerization of Bcl-2 with Bax. This leads to increased formation of Bax homodimers and disruption of the mitochondrial membrane, thereby inducing apoptosis.

function by producing ribose-5-phosphate for DNA synthesis and repair and also by augmenting antioxidant capacity by the generation of NADPH. The PPP is divided into oxidative and nonoxidative branches, with the former consisting of three irreversible reactions that generate NADPH and pentose phosphates (169). The supply of glucose 6-phosphate toward the PPP instead of glycolysis depends on specific intracellular requirements (309). The nonoxidative branch of the pathway reconverts pentose phosphates into glycolytic intermediates (reversible), although ATP is not directly produced. In the process, thiamine (vitamin B_1) acts as a cofactor for transketolase, the rate-limiting enzyme of the nonoxidative branch of the PPP (257). However, diabetes is a thiamine-deficient state, and such individuals can display decreased transketolase activity and PPP activation (234). In agreement with this notion, we found that PPP activation offered significant potential as a therapeutic agent for acute myocardial infarction under hyperglycemic conditions (191, 192). Although such findings are promising, additional studies are required to determine the precise sequence of NOGP activation and interpathway cross talk to target the those that are activated earliest.

To gain further insight into the relative importance and degree of activation of the respective NOGPs, we performed a comparative analysis on original data generated from our recent publication (192). We adopted this approach because all NOGPs were assessed in the same model of ischemia-reperfusion under hyperglycemic conditions. Our data revealed that the AGE pathway is robustly upregulated compared with the others and is thus emerging as a key thera-

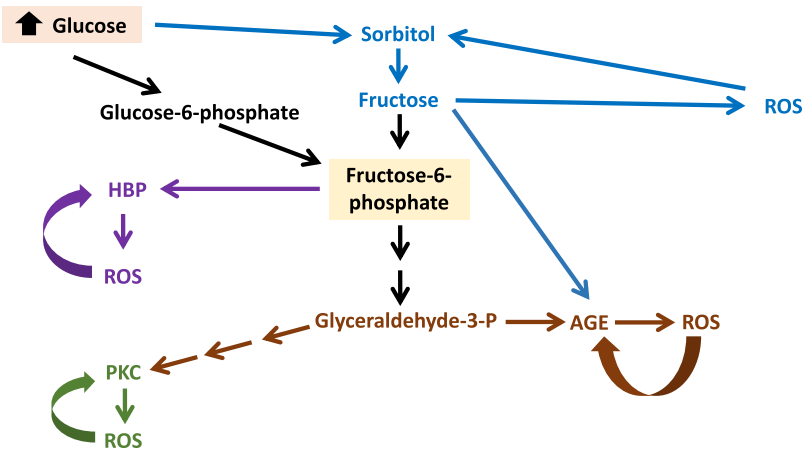

Fig. 6. A model to demonstrate the metabolic vicious cycle whereby hyperglycemia-mediated stimulation of NOGPs fuels oxidative stress and further NOGP activation. The ROS produced by activation of the various NOGPs play a central role in fueling this vicious metabolic cycle. ROS produced by each pathway will further stimulate the respective NOGP as indicated while also fueling the other NOGPs. The ROS produced will inhibit flux through the glycolytic pathway to further increase NOGP activation. In addition, higher ROS levels will deplete glutathione (GSH) and thus increase polyol pathway flux. Greater ROS availability will result in glucose autoxidation and lipid peroxidation that will generate increased AGEs. Increased ROS such as H_2O_2 can also directly cause activation of PKC. In addition, the polyol pathway plays a key role by activating other NOGPs. Here it can generate fructose that can be further metabolized to produce AGEs and fructose-6-phosphate, which can lead to activation of the HBP, PKC and AGEs.

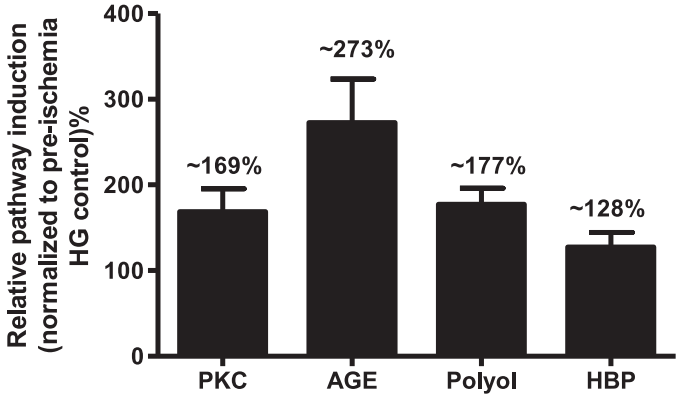

Fig. 7. Comparative analyses of NOGP activation in response to ischemia-reperfusion under hyperglycemic conditions. Relative NOGP activation with ischemia-reperfusion under hyperglycemic conditions on the basis of data generated from our recently published work (192). The relative pathway induction was calculated as a percentage of preischemic hyperglycemia and determined by using specific inhibitors of each respective pathway. Values are expressed as means ± SE (n = 6). HG, hyperglycemia.

peutic target (Fig. 7). Additional analyses have also demonstrated that the AGE pathway was induced relatively early in response to hyperglycemic perfusions before the onset of ischemia-reperfusion. The AGE pathway is thus a crucial mediator of cardiac pathology under hyperglycemic conditions because it can trigger both systemic and intracellular sequelae. AGEs can exert multiple effects such as altering the function of both intracellular proteins and extracellular matrix proteins while also modifying plasma proteins that are able to bind to RAGE on target cells [reviewed in Giacco and Brownlee (105)]. As was discussed earlier in this review article, the AGE-RAGE pathway can act on various heart cell types including cardiomyocytes, endothelial cells, fibroblasts, and vascular smooth muscle cells. Such interactions can trigger damaging effects (e.g., AGE-LDL exposure elicited oxidative stress and a proinflammatory state in human endothelial cells) (290). To support this concept, glycated serum albumin supply has resulted in ROS production in endothelial cells that was likely due to an upregulation of Nox4 expression (249). This is unlike the other NOGPs that are dependent on high glucose uptake into target cells for its activation (Fig. 1). In this instance vascular and cardiac endothelial cells, unlike cardiomyocytes, are the major target because they do not have any requirements for insulin-mediated glucose uptake (37, 158). Endothelial cell dysfunction will lead to serious consequences for cardiac function when cross talk exists between heart cell types [reviewed in Zhang and Shah (341)]. For example, the protective effects of endothelial cells on heart function can be abolished by excess glucose availability (175).

The AGE pathway emerges as an early therapeutic target for diabetes-related CVD onset with multiple effects on various target cells. It is also our proposal that inactivation of the AGE pathway will blunt downstream effects that include the coordinate activation of PKC, the HBP, and the polyol pathway (Fig. 8). Therefore, with this gap in the current management of diabetes and associated CVD, it is important to *1*) perform additional investigations to evaluate the role of NOGPs within the clinical setting in view of the limited studies that have been undertaken so far, and *2*) pursue the development of drugs that address the fundamental pathophysiological abnormalities that link diabetes/hyperglycemia and CVD in which the AGE pathway emerges as a crucial target (76).

ACKNOWLEDGMENTS

We thank Dr. Uthra Rajamani for assisting with the design of Fig. 5.

GRANTS

This work was supported by the National Research Foundation of South Africa and Stellenbosch University.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: R.F.M. and M.F.E. prepared figures; R.F.M. and M.F.E. drafted manuscript; R.F.M. and M.F.E. edited and revised manuscript; R.F.M. and M.F.E. approved final version of manuscript.

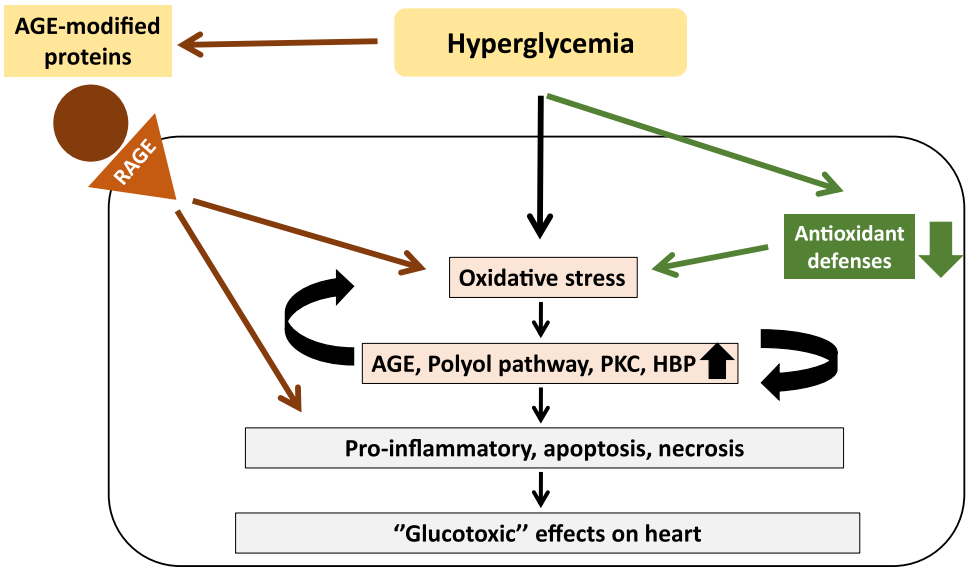

Fig. 8. Convergence of downstream effects of hyperglycemia on cardiac endothelial cells. Increased glucose availability results in the generation of higher oxidative stress (increased rate of production as well as decreased antioxidant surveillance), which activates NOGPs. Greater NOGP stimulation can further increase ROS and as such, pathways are interlinked and its activation will enhance NOGP flux as part of this metabolic vicious cycle. Hyperglycemia can also trigger systemic effects and lead to glycation of circulating proteins that can bind to an AGE receptor (RAGE) and trigger oxidative stress and inflammation. We propose that the majority of the NOGP effects culminate on endothelial cells because glucose uptake is not mediated by glucose transporters in this instance. End effects include inflammation, oxidative stress, cell death, and glucotoxic effects, particularly on the microvasculature.

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