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Forum Review

Increased Sorbitol Pathway Activity Generates Oxidative Stress in Tissue Sites for Diabetic Complications

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ABSTRACT

Chronic diabetic complications, in particular, nephropathy, peripheral and autonomic neuropathy, "diabetic foot," retinopathy, and cardiovascular disease, remain the major cause of morbidity and mortality in patients with diabetes mellitus. Growing evidence indicates that both increased activity of the sorbitol pathway of glucose metabolism and enhanced oxidative stress are the leading factors in the pathogenesis of diabetic complications. The relation between the two mechanisms remains the area of controversy. One group has reported that increased sorbitol pathway activity has a protective rather than detrimental role in complication-prone tissues because the pathway detoxifies toxic lipid peroxidation products. Others put forward a so-called "unifying hypothesis" suggesting that activation of several major pathways implicated in diabetic complications (*e.g.,* sorbitol pathway) occurs due to increased production of superoxide anion radicals in mitochondria and resulting poly(ADP-ribose) polymerase activation. This review (a) presents findings supporting a key role for the sorbitol pathway in oxidative stress and oxidative stress-initiated downstream mechanisms of diabetic complications, and (b) summarizes experimental evidence against a detoxifying role of the sorbitol pathway, as well as the "unifying concept." *Antioxid. Redox Signal.* 7, 1543–1552.

INTRODUCTION

The sorbitol pathway of glucose metabolism consists of two reactions. First, glucose is reduced to its sugar alcohol sorbitol by NADPH-dependent aldose reductase (AR), and then sorbitol is oxidized to fructose by NAD-dependent sorbitol dehydrogenase (SDH) (see Fig. 1). Direct negative consequences of the sorbitol pathway hyperactivity under diabetic or hyperglycemic conditions include intracellular sorbitol accumulation and resulting osmotic stress (41, 49), and generation of fructose, which is a 10 times more potent glycation agent than glucose (108). Other direct biochemical consequences of increased sorbitol pathway activity have not been clearly identified. One group reported that increased flux through SDH leads to so-called "pseudohypoxia" (113), *i.e.,* an increased free cytosolic NADH/NAD^+ ratio in heart, retina, and peripheral nerve of rats with experimental diabetes (113), whereas others (77, 78, 82) failed to find such a relation in tissues other than lens (77). Diabetes-related depletion of NADPH (a cofactor of the AR reaction) has never been documented in diabetic kidney, peripheral nerve, heart, and retina. The lens data are contradictory (52, 56), and the decrease in NADPH concentration found by one group (52) is very modest (~15%). Note, that the aforementioned studies assessed total (*i.e.,* both free and protein-bound) NADPH and that only a small fraction of the total cellular pool of NADPH (*i.e.,* free NADPH) participates in the catalysis (*i.e.,* glutathione reductase reaction). No methodology for assessment of free NADPH in animal tissues is currently available.

Indirect biochemical consequences of increased sorbitol pathway activity include the following: (a) nonenzymatic glycation initiated by fructose, the product of the SDH reaction, its product fructose 3-phosphate, and other precursors of advanced glycation endproducts (AGEs); (b) activation of protein kinase C (PKC); (c) oxidative and nitrosative stress; and (d) oxidative stress-mediated downstream events, *i.e.,* activa-

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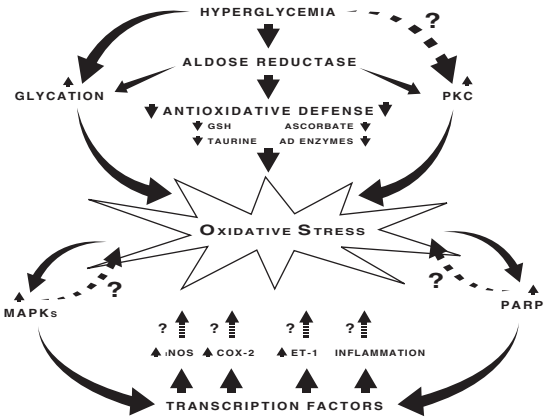

FIG. 1. Sorbitol pathway of glucose metabolism and direct negative consequences of its activation in tissue sites for diabetic complications.

tion of mitogen-activated protein kinases (MAPKs) and poly(ADP-ribose) polymerase (PARP; Fig. 2). The important role for the sorbitol pathway in initiation of nonenzymatic glycation is supported by findings of several groups indicating that AR inhibitor (ARI) treatment prevents formation of AGEs, *i.e.,* pentosidine (66) and carboxymethyllysine (30), and their precursors, *i.e.,* fructose 3-phosphate (50), methylglyoxal (92), and 3-deoxyglucosone (29, 69). At least, four reports (39, 44, 68, 115) support the important role of AR in activation of PKC, *e.g.,* in vascular cells (115). Activation of PKC in hyperglycemic/diabetic conditions occurs due to increased formation of the PKC activator diacylglycerol from α-glycerophosphate under conditions of AR-dependent suppression of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase. AR inhibition restores normal glycolytic flux (71, 74) and prevents increased formation of α-glycerophosphate (71) and diacylglycerol (44). Both nonenzymatic glycation and activation of PKC contribute to oxidative stress via free radical generation during AGE interaction with AGE receptors (RAGE) and phosphorylation (activation) of the superoxide-generating enzyme, NAD(P)H oxidase, respectively (1, 6, 38, 116). Thus, increased AR activity can contribute to oxidative stress by promoting glycation and PKC activation. However, numerous findings suggest that the major contribution of increased AR activity to oxidative stress is a disruption of antioxidative defense mechanisms independent of either glycation or PKC activation.

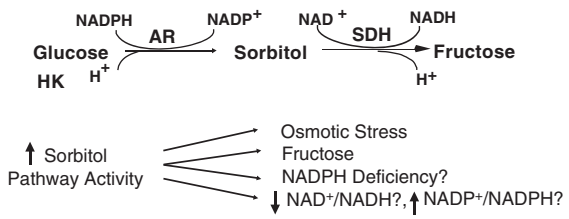

FIG. 2. Pathways and mechanisms involved in the relation between increased AR activity and oxidative stress in diabetes mellitus.

Furthermore, AR-mediated oxidative stress leads to such detrimental consequences as MAPK activation (4, 94) and PARP activation (86, 87, 90). Taking into consideration that MAPKs and PARP control numerous transcription factors (8, 28, 120), one would expect that AR is linked to downstream up-regulation of inflammatory genes, cell adhesion molecules, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and endothelin-1 (ET-1) (63, 120). Some of these downstream events, *e.g.,* activation of iNOS (118) and COX-2 (33), further exacerbate oxidative stress. Experimental findings supporting the role for increased AR activity in such manifestations of oxidative stress as (a) superoxide generation, (b) lipid peroxidation, (c) depletion of the major biological antioxidant, reduced glutathione (GSH), (d) depletion of other important antioxidants, ascorbate and taurine, (e) down-regulation of antioxidative defense enzyme activities, (f) peroxynitrite-induced injury (nitrosative stress), as well as such downstream events as MAPK activation and PARP activation, are provided below.

According to the "unifying hypothesis," mitochondrial superoxide production is a primary mechanism responsible for activation of four major pathways involved in diabetic complications, *i.e.,* nonenzymatic glycation, PKC, hexosamine pathway, and sorbitol pathway (9). Whereas the role for oxidative stress in diversion of the glycotic flux toward the formation of methylglyoxal and diacylglycerol is beyond doubt, free radicals are not necessarily generated in mitochondria; such nonmitochondrial mechanisms as xanthine oxidase and NAD(P) oxidase are also of great importance (18, 20, 61). Furthermore, several groups failed to find any suppression of the sorbitol pathway activity by superoxide scavengers such as lipoic acid (47, 76, 81, 107), taurine (75, 81, 93), and the metal chelator hydroxyethyl starch deferoxamine (17). At the same time, it was demonstrated that increased AR activity contributes to superoxide production in high glucose-exposed vascular cells and tissues of diabetic rats. ARIs zopolrestat (27) and fidarestat (88) were found to prevent aortic superoxide formation assessed by the lucigenin chemiluminescence test. AR inhibition reduced superoxide formation and dichlorofluorescein fluorescence (a measure of intracellular hydrogen peroxide, a product of superoxide dismutase) in high glucose-exposed bovine aortic and retinal endothelial cells, as well as retinal pigment epithelial cells (21, 72, 85). Retinal epithelial cells stably transfected with the AR gene and cultured in hyperglycemic conditions had increased dichlorofluorescein fluorescence compared with parental cells with normal AR content (72). Of interest, intracellular superoxide formation has been induced by the nonmetabolizable glucose analogue 3-methyl-*O*-glucose (21), which supports the role for intracellular osmotic stress in superoxide formation. In the same study, superoxide formation was greater in cells cultured in high-glucose medium than in cells cultured with equimolar concentrations of 3-methyl-*O*-glucose, which indicates that either osmotic stress is not the only factor in hyperglycemia-induced intracellular superoxide formation, or accumulation of sorbitol, the product of glucose metabolism, results in a more severe osmotic stress than accumulation of equimolar quantities of 3-methyl-*O*-glucose. The role of osmotic stress in high glucose-induced oxidative stress in ocular lens has been previously demonstrated in our experiments

with an SDH inhibitor administered *in vivo* to diabetic rats (77, 78). Further studies are needed to sort out how osmotic stress contributes to oxidative stress; for example, the role of intracellular osmotic stress in control of free radical-generating [*i.e.,* xanthine oxidase, NAD(P)H oxidase] and antioxidative defense enzymes has never been explored.

A number of studies support the role of AR in enhanced lipid peroxidation in tissue sites for diabetic complications. AR inhibition achieved with several structurally diverse ARIs, *i.e.,* sorbinil, [5-(3-thienyl)tetrazol-1-yl]acetic acid (TAT), and, recently, fidarestat, was found to counteract accumulation of lipid peroxidation products, malondialdehyde and 4-hydroxyalkenals, in tissue sites for diabetic complications, including lens (74, 99, 117), peripheral nerve (57, 83), and retina (85). These inhibitor studies are consistent with the findings in mice expressing human AR gene in the lens: diabetic transgenic mice had greater lens malondialdehyde content than diabetic mice with normal AR content (51).

In contrast to the aforementioned findings, one group has reported that AR inhibition leads to further exacerbation of diabetes-associated accumulation of the lipid peroxidation products, 4-hydroxyalkenals (96). It has been suggested that AR participates in the detoxification process by metabolizing those highly reactive and toxic substances. However, this concept has several major weaknesses. First, the products of α,β-unsaturated aldehyde, 4-hydroxyalkenal, metabolism by AR, *i.e.,* glutathione-4-hydroxynonenal conjugate, 1,4-dihydroxy-2-nonene, and 4-hydroxy-2-nonenoic acid, have never been identified *in vivo* in tissue sites for diabetic complications. The presence of these products has only been demonstrated in studies in *in situ* perfused organs (101, 105) or incubated tissues (104) that used relatively high concentrations of 4-hydroxynonenal (100–200 μ*M*). Second, whereas antioxidant deficiency or administration of prooxidants to nondiabetic animals has been shown to result in diabetes-like complications, *e.g.,* neuropathy (12, 37) and some manifestations of retinopathy (98), administration of ARIs did not cause such effects (67, 109). ARI-treated non-diabetic animals preserved normal peripheral nerve function (67, 109), as well as retinal vascular endothelial growth factor expression (85) known to be increased under conditions of enhanced oxidative stress, *e.g.,* in diabetes (10, 81, 102). Third, if ARI administration exacerbated oxidative stress, one would expect to see the "synergistic" effect of diabetes and ARI treatment on diabetic complications, *i.e.,* accelerated development of pathologic changes in ARI-treated compared with untreated diabetic animals. However, it is well known that AR inhibition delays, prevents, and, at early stages, reverses diabetic complications.

The pathogenetic role of increased AR activity in chronic diabetic complications has been summarized in several recent reviews (70, 73), and supported by at least five lines of evidence: (a) similarity of functional, metabolic, and morphological abnormalities characteristic for diabetic complications in animal models of diabetes and galactose feeding (41, 43, 97); (b) studies with structurally diverse ARIs (41, 43, 67, 70, 73, 83, 85, 97, 109); (c) studies in AR-overexpressing animals (51, 103, 114); (d) identification of high AR protein level as an independent risk factor for diabetic complications in patients with both type 1 (insulin-dependent) and type 2 (non–insulin-dependent) diabetes mellitus (40); and (e) genetic polymorphism data (31, 70) revealing increased frequency of the Z-2 allele of the AR gene, known to be associated with two- to threefold AR expression (70) in patients with diabetic complications compared with the uncomplicated group. The role of increased AR activity in the pathogenesis of peripheral diabetic neuropathy is also supported by recent clinical trials with two ARIs, zenarestat (26) and the most potent and low-toxic inhibitor, fidarestat (36). In the zenarestat study (26); robust inhibition of AR in diabetic human nerve resulted in improvement of both nerve physiology and fiber density. The results of two double-blind placebo-controlled clinical trials of fidarestat in patients with type 1 and type 2 diabetes are also encouraging (26; and Arezzo *et al.,* unpublished observations). In the Japanese study (36), fidarestat improved electrophysiological measures of median and tibial motor nerve conduction velocity, F-wave minimum latency, F-wave conduction velocity, and median sensory nerve conduction velocity (forearm and distal), as well as subjective symptoms of peripheral diabetic neuropathy such as numbness, spontaneous pain, sensation of rigidity, paresthesia in the sole upon walking, heaviness in the foot, and hypesthesia. The improvement of nerve function with AR inhibition has also been observed in the U.S. study, which is still in progress.

Evidence from at least seven groups suggests that the sorbitol pathway hyperactivity has a key role in hyperglycemia-induced GSH depletion in the peripheral nerve (14, 65, 72, 78, 107), lens (51, 56, 74–77) and smooth muscle cells (68). AR inhibition was found to prevent (56) or reverse (65, 74, 83) GSH depletion. The diabetic mice expressing human AR gene in the lens had lower lens GSH concentration than diabetic mice with normal AR content (51). The diabetic mice selectively overexpressing AR in Schwann cells of the peripheral nerve clearly manifested nerve GSH depletion, whereas their diabetic wild-type littermates preserved normal GSH levels (103). AR knockout mice have been protected from GSH depletion, in the peripheral nerve. The mechanism underlying the inverse relation between AR activity and intracellular GSH concentrations remains unidentified. At least two groups have suggested that hyperglycemia-induced GSH deficiency *e.g.,* in the peripheral nerve, results from depletion of NADPH, a cofactor shared by AR and glutathione reductase, and the resulting slowing of the glutathione redox cycle (14, 51). However, this concept is not supported by the absent or minor reciprocal increase of oxidized glutathione (GSSG) concentration in concert with the decrease in GSH in diabetic nerve (14, 65, 107), lens (75–77), and kidney (84). In addition, as has already been stated, NADPH deficiency in the diabetic peripheral nerve has never been documented. Furthermore, whereas diabetes-associated GSH depletion in such targets as ocular lens reaches 80% (51, 56, 74–77), NADPH depletion is minor (52) or absent (56). Apparently, GSH depletion in target tissues for diabetic complications, *i.e.,* lens, peripheral nerve, and renal cortex, is due to a decrease in total glutathione rather than impairment of the NADPH-dependent reduction of GSSG to GSH. Note that AR activity manifested by sorbitol accumulation is greater in the diabetic rat retina than in renal cortex; however, no retinal GSH depletion has been detected in short-term diabetic rats (2, 81, 85). The key role of "NADPH deficiency" is also not supported by studies

with SDH inhibitors (SDIs). Administration of SDI doses of 50–250 mg/kg/day to diabetic rats resulted in sorbitol accumulation above the "diabetic threshold" in the peripheral nerve (13, 78), as well as the lens (24, 77), and exacerbated GSH depletion in both tissues (77, 78). Therefore, sorbitol accumulation-linked osmotic stress rather than NADPH deficiency with resulting slowing of the glutathione redox cycle is responsible for diabetes-induced GSH depletion in the lens and peripheral nerve. This conclusion does not contradict the concept of "decreased glutathione biosynthesis" because osmotic stress can disrupt GSH biosynthesis by affecting uptake of the amino acid cysteine, the rate-limiting step in GSH biosynthesis. However, the "osmotic concept" is not supported by studies in diabetic AR-overexpressing SDH-knockout (AR^+/SDH^-) mice that developed higher lens sorbitol accumulation, but less manifested GSH depletion than diabetic AR-overexpressing mice with normal SDH content (AR^+/SDH^+) (S.K. Chung, unpublished observations).

Some investigators suggest that hyperglycemia-induced GSH depletion occurs due to glycation or decreased expression of the key enzyme of glutathione biosynthesis, γ-glutamylcysteine synthetase (111), and glycation of glutathione reductase (7). However, the role of glycation/glycoxidation in diabetes-associated inhibition of GSH biosynthesis is not supported by studies demonstrating (a) the lack of any antioxidant activity of the inhibitor of nonenzymatic glycation, aminoguanidine, in the peripheral nerve of diabetic rats (45), (b) the lack of any correction of GSH depletion or decrease of GSH/cysteine ratio, the index of the rate of glutathione biosynthesis, in the retina of aminoguanidine-treated diabetic rats versus untreated diabetic group (3), and (c) exacerbation rather than correction of diabetes-induced GSH depletion in lens and peripheral nerve by SDI treatment (24, 77, 78) that did not affect intracellular glucose and markedly reduced intracellular fructose concentrations (24, 77, 78). Of interest, one group (89) found that aminoguanidine inhibits catalase and generates hydrogen peroxide *in vitro*. The latter is in contrast with the study by Giardino *et al.* (25) who described antioxidant effects of aminoguanidine in retinal Muller cells exposed to 10 μ*M* hydrogen peroxide. Antioxidant properties of aminoguanidine in the diabetic retina have been described by Kowluru *et al.* (48); however, the retinal GSH concentrations in the aforementioned study are at least threefold higher than those reported by four other groups (23). No antioxidant properties of aminoguanidine have been revealed in another study that, in addition to thiobarbituric acid reactive substances, used the most specific and sensitive marker of lipid peroxidation, *i.e.,* F_2-isoprostane (95).

It has also been reported that glyoxals, reactive α-oxoaldehydes formed in excessive amounts from glucose in hyperglycemic conditions, increase the susceptibility of GSH to oxidation by hydrogen peroxide (100). However, this is unlikely to be the mechanism for GSH depletion in tissues of diabetic animals because of the lack of accumulation or very minor increase of the oxidized form of glutathione, GSSG.

Along with GSH, other nonenzymatic antioxidants provide antioxidative defense in tissue sites for diabetic complications, and vitamin C (ascorbate), taurine and α-tocopherol are the most important. Note that diabetes-induced α-tocopherol depletion has not been documented in tissues developing diabetic complications. The studies of our group revealed that total and free ascorbic acid (AA) concentrations are decreased and dehydroascorbate (DHAA)/AA ratio increased in the peripheral nerve (80, 83) and kidneys (84), but not retina (23, 81, 85), of diabetic rats. AA has an important role in antioxidative defense and, in particular, phenoxyl radical neutralization and α-tocopherol recycling. Diabetic subjects, particularly patients with poor glycemic control, have decreased plasma AA concentrations and increased AA oxidation to DHAA (55). The mechanisms of AA depletion in tissue sites for diabetic complications have not been studied in detail. However, reports (55, 83, 99) suggest that AA concentrations are inversely related to the sorbitol pathway activity. The study of our group (77) suggests that AA depletion in the diabetic precataractous lens is mediated by sorbitol accumulation and intralenticular osmotic stress but not by nonenzymatic glycation. Lens AA concentrations are reduced by L-buthionine (*S,R*)-sulfoximine, an inhibitor of glutathione biosynthesis, because GSH and other cellular thiols play an important role in vitamin C homeostasis by regenerating AA from DHAA and semiascorbyl radicals. Therefore, it is not surprising that the changes in the glutathione and ascorbate systems of antioxidative defense have been reported to occur in parallel. So far, it is unclear whether AA depletion in tissues of diabetic animals is a primary response or a secondary phenomenon occurring due to depletion of GSH, because GSH concentrations are also decreased in major sites for diabetic complications, including lens, peripheral nerve, and kidneys. Both diabetes-induced GSH and ascorbate depletion in peripheral nerve and lens is reversed by an ARI treatment (56, 71, 72, 74, 83, 99, 107). However, the glutathione and ascorbate systems of antioxidative defense could respond differently to some experimental conditions, *e.g.,* to the treatment with another antioxidant, taurine. In our study (80), normal total and free AA concentrations and the ascorbate redox state, but not GSH concentrations, were preserved in the peripheral nerve of diabetic rats fed a taurine-supplemented diet. Apparently, this effect of exogenous taurine is not mediated via ascorbate regeneration by GSH, or an osmotic mechanism, because nerve sorbitol concentrations were similar in diabetic rats fed taurine-supplemented and regular diets (93).

Growing evidence indicates that increased AR activity has a major role in diabetes-induced depletion of another endogenous nonenzymatic antioxidant, taurine. Taurine is the most abundant amino acid in mammalian tissues that acts as (a) osmolyte, (b) neurotransmitter, (c) membrane stabilizer, (d) modulator of Ca^{2+} homeostasis, (e) regulator of PKC-dependent phosphorylation, and (f) endogenous antioxidant. Taurine depletion has been documented in such tissues of diabetic animals as lens (75), peripheral nerve (80, 93), kidney (110), but not retina (81). The mechanism(s) of antioxidant activity of taurine remains poorly understood although the ability of taurine to decrease diabetes-induced lipid peroxidation has been demonstrated in the peripheral nerve (80), kidneys (110), lens (75), retina (81), liver, and pancreas (54). Both taurine and hypotaurine scavenge hypochlorite (5, 19), which is known to form from hydrogen peroxide in the presence of Cu^{2+}, *i.e.,* under conditions of diabetes-associated transition metal imbalance, and is involved in inflammation. Recently, it has been demonstrated (32) that hypochlorite also

reacts with superoxide anions to yield highly reactive hydroxyl radicals. Thus, taurine, the hypochlorite scavenger, counteracts hydroxyl radical formation. Spin-trapping experiments (46) have revealed that taurine scavenges superoxide. In addition, taurine accelerates catabolism of norepinephrine, which can autoxidize and thus contribute to reactive oxygen species (ROS) generation (15). Thus, taurine appears to be involved in both protection against formation of the most reactive ROS and their neutralization. Several studies, including those from our group, suggest that taurine interferes with several components of antioxidative defense. Erdem *et al.* (22) have demonstrated the ability of taurine to activate superoxide dismutase. We have demonstrated that the antioxidant effects of taurine in the diabetic peripheral nerve (80), but not retina (81), are, at least in part, mediated through the ascorbate system of antioxidative defense, *i.e.,* increase in free AA concentrations and AA/DHAA ratio. Taurine deficiency-mediated oxidative stress is responsible for decreased nerve growth factor expression in the diabetic nerve (80). In turn, nerve growth factor deficiency is known to be associated with increased ROS formation (62), potentially due to down-regulation of superoxide dismutase and catalase. Thus, taurine deficiency in tissue sites for diabetic complications creates "vicious cycles" resulting in further progression of oxidative damage. The studies of two groups implicate increased AR activity and resulting intracellular osmotic stress in taurine depletion in high glucose-exposed retinal pigment epithelial cells (106) and lens of galactose-fed rats (60). In both cases, taurine deficiency was effectively prevented by an ARI treatment.

Our group has generated evidence that increased AR activity impairs antioxidative defense provided by several antioxidative defense enzymes, including superoxide dismutase, glutathione peroxidase, glutathione reductase, and glutathione transferase in diabetic retina (85) and peripheral nerve (79). The mechanism(s) of this phenomenon remains unclear. Another study (34) has shown that AR activity may affect gene expression of such antioxidative enzymes as catalase, Cu,Zn-superoxide dismutase, and glutathione peroxidase in subjects with diabetic nephropathy.

Numerous findings indicate that nitrosative stress, *i.e.,* increased formation of the potent oxidant peroxynitrite ($ONOO^-$) and subsequent nitration or nitrosylation of cell components, plays an important role in a number of pathological conditions associated with oxidative stress (58, 112). Evidence for the presence of nitrosative stress in both experimental and clinical diabetic neuropathy (16, 35) and other diabetic complications (88, 91) is emerging. Peroxynitrite is formed in the reaction of superoxide anion radicals with nitric oxide; therefore, any mechanisms contributing to superoxide and nitric oxide generation are also responsible for increased production of reactive nitrogen species. It is not surprising, therefore, that AR inhibition with zopolrestat was found to counteract accumulation of nitrotyrosine, a marker of peroxynitrite-induced injury, in high glucose-exposed endothelial cells (21). We observed a similar phenomenon with another ARI, fidarestat, that counteracted diabetes-associated increase in nitrotyrosine immunoreactivity in peripheral nerve, retina, as well as glomerular and tubular compartments of renal cortex (88; Obrosova *et al.,* unpublished observations). Suppression of nitrotyrosine immunoreactivity by fidarestat has also been found in epineurial arterioles isolated from sciatic nerve of the ARI-treated streptozotocin (STZ)-diabetic rats (88).

Recent findings reveal that increased sorbitol pathway activity activates mechanisms localized further downstream from oxidative stress in the pathogenesis of diabetic complications, *i.e.,* MAPKs (4) and PARP (88). Evidence for the pathogenetic role of both mechanisms is emerging (4, 63, 86, 87, 90, 94). PARP activation has been demonstrated to play a major role in diabetes-associated endothelial and myocardial dysfunction (90). Both MAPKs and PARP are the fundamental mechanisms in the pathogenesis of peripheral diabetic neuropathy (4, 86, 94), and MAPK activation in dorsal root ganglia neurons of STZ-diabetic rats was reversed by an ARI treatment (4). According to the "unifying hypothesis," mitochondrial superoxide-induced PARP activation in hyperglycemic and diabetic conditions accounts for down-regulation of the glyceraldehyde-3-phosphate dehydrogenase reaction of glycolysis, and thus feedback inhibition of the upstream reactions of the glycolytic pathway by increased concentrations of glyceraldehyde 3-phosphate (9). Increased availability of glucose due to inhibition of its phosphorylation by hexokinase is in turn responsible for sorbitol pathway activation (9). Based on this premise, one would expect that PARP inhibitors decrease glucose and sorbitol pathway intermediate accumulation in tissue sites for diabetic complications. However, our group failed to produce such observation with three structurally diverse PARP inhibitors, *i.e.,* 3-aminobenzamide, 1,5-isoquinolinediol, and PJ34 [*N*-(6-oxo-5,6-dihydrophenanthridin-2-yl)-*N,N*-dimethylacetamide], which did not counteract glucose, sorbitol, and fructose accumulation in either retina (87) or peripheral nerve (53) of STZ-diabetic rats. Furthermore, AR inhibition with fidarestat was found to counteract diabetes-associated accumulation of poly(ADP-ribose), the product of PARP activation, in peripheral nerve, retina, and glomerular and tubular compartments of renal cortex (88). This is consistent with our observations with a peroxynitrite decomposition catalyst in the model of experimental diabetic neuropathy (88) indicating that peroxynitrite is a major contributor to PARP activation in the diabetic nerve. Therefore, any compound counteracting formation of reactive nitrogen species should also suppress poly(ADP-ribose) accumulation. Fidarestat does not have PARP-inhibiting properties tested in the cell-free system containing PARP and NAD^+.

It is noteworthy that whereas MAPK activation and PARP activation occur downstream from oxidative injury, both mechanisms have also been reported to exacerbate oxidative stress. In some circumstances, MAPK activation contributes to ROS generation (64), and PARP activation increases lipid peroxidation (119). On the one hand, this is not surprising because some downstream effectors of PARP activation, *i.e.,* COX-2 (42, 43), iNOS (118), and ET-1 (11), contribute to oxidative damage. Moreover, the heme-containing protein myeloperoxidase, released from stimulated polymorphonuclear leukocytes at sites of inflammation, a generally accepted consequence of PARP activation, is involved in generation of ROS and reactive nitrogen species. On the other hand, contribution of these downstream mechanisms to

oxidative stress in some tissue sites for diabetic complications, such as vascular endothelium, peripheral nerve, retina, and kidneys, is probably minimal because the PARP inhibitors, PJ34 and 1,5-isoquinolinediol, completely suppress PARP activation, but do not counteract nitrotyrosine formation in aorta, peripheral nerve, retina, and kidneys, as well as superoxide and nitrotyrosine formation in epineurial vessels of STZ-diabetic rats (88; Obrosova *et al.,* unpublished observations).

In conclusion, increased sorbitol pathway activity leads to oxidative stress in tissue sites for diabetic complications. This occurs primarily due to disruption of antioxidative defense and, in particular, depletion of three nonenzymatic antioxidants: GSH, ascorbate, and taurine. Biochemical mechanisms underlying antioxidant depletion require further studies. In addition, the pathway contributes to activation of other important mechanisms, such as nonenzymatic glycation and activation of PKC, that are involved in free radical generation. Such consequences of oxidative injury as activation of MAPKs, PARP, and downstream effectors of both mechanisms could theoretically exacerbate oxidative stress, although further studies are needed to confirm that this occurs indeed in diabetes.

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ABBREVIATIONS

AA, ascorbic acid; AGE, advanced glycation end product; AR, aldose reductase; ARI, aldose reductase inhibitor; COX-2, cyclooxygenase-2; DHAA, dehydroascorbic acid; ET-1, endothelin-1; GSH, reduced glutathione; GSSG, oxidized glutathione; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; PARP, poly(ADP-ribose) polymerase; PKC, protein kinase C; ROS, reactive oxygen species; SDH, sorbitol dehydrogenase; SDI, sorbitol dehydrogenase inhibitor; STZ, streptozotocin.

REFERENCES

1. Abiko T, Abiko A, Clermont AC, Shoelson B, Horio N, Takahashi J, Adamis AP, King GL, and Bursell SE. Characterization of retinal leukostasis and hemodynamics in insulin resistance and diabetes: role of oxidants and protein kinase-C activation. *Diabetes* 52: 829–837, 2003.
2. Agardh CD, Agardh E, Qian Y, and Hultberg B. Glutathione levels are reduced in diabetic rat retina but are not influenced by ischemia followed by recirculation. *Metabolism* 47: 269–272, 1998.
3. Agardh E, Hultberg B, and Agardh C. Effects of inhibition of glycation and oxidative stress on the development of cataract and retinal vessel abnormalities in diabetic rats. *Curr Eye Res* 21: 543–549, 2000.
4. Agthong S and Tomlinson DR. Inhibition of p38 MAP kinase corrects biochemical and neurological deficits in experimental diabetic neuropathy. *Ann N Y Acad Sci* 973: 359–362, 2002.
5. Aruoma OI, Halliwell B, Hoey BM, and Butler J. The antioxidant action of taurine, hypotaurine and their metabolic precursors. *Biochem J* 256: 251–255, 1988.
6. Bierhaus A, Schiekofer S, Schwaninger M, Andrassy M, Humpert PM, Chen J, Hong M, Luther T, Henle T, Kloting I, Morcos M, Hofmann M, Tritschler H, Weigle B, Kasper M, Smith M, Perry G, Schmidt AM, Stern DM, Haring HU, Schleicher E, and Nawroth PP. Diabetes-associated sustained activation of the transcription factor nuclear factor-kappaB. *Diabetes* 50: 2792–2808, 2001.
7. Blakytny R and Harding JJ. Bovine and human alpha-crystallins as molecular chaperones: prevention of the inactivation of glutathione reductase by fructation. *Exp Eye Res* 64: 1051–1058, 1997.
8. Bogatcheva NV, Dudek SM, Garcia JG, and Verin AD. Mitogen-activated protein kinases in endothelial pathophysiology. *J Investig Med* 51: 341–352, 2003.
9. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 414: 813–820, 2001.
10. Caldwell RB, Bartoli M, Behzadian MA, El-Remessy AE, Al-Shabrawey M, Platt DH, and Caldwell RW. Vascular endothelial growth factor and diabetic retinopathy: pathophysiological mechanisms and treatment perspectives. *Diabetes Metab Res Rev* 19: 442–455, 2003.
11. Callera GE, Touyz RM, Teixeira SA, Muscara MN, Carvalho MH, Fortes ZB, Nigro D, Schiffrin EL, and Tostes RC. ETA receptor blockade decreases vascular superoxide generation in DOCA-salt hypertension. *Hypertension* 42: 811–817, 2003.
12. Cameron NE, Cotter MA, Archibald V, Dines KC, and Maxfield EK. Anti-oxidant and pro-oxidant effects on nerve conduction velocity, endoneurial blood flow and oxygen tension in non-diabetic and streptozotocin-diabetic rats. *Diabetologia* 37: 449–459, 1994.
13. Cameron NE, Cotter MA, Basso M, and Hohman TC. Comparison of the effects of inhibitors of aldose reductase and sorbitol dehydrogenase on neurovascular function, nerve conduction and tissue polyol pathway metabolites in streptozotocin-diabetic rats. *Diabetologia* 40: 271–281, 1997.
14. Cameron NE, Cotter MA, Jack AM, Basso MD, and Hohman TC. Protein kinase C effects on nerve function, perfusion, Na^+,K^+-ATPase activity and glutathione content in diabetic rats. *Diabetologia* 42: 1120–1130, 1999.
15. Chabine R, Hanna J, Abou Khalil K, Cheav SL, Hatala R, Bouchi N, and Mounayar A. Taurine and myocardial noradrenaline. *Arzneimittel forschung* 44: 126–128, 1994.
16. Coppey LJ, Gellett JS, Davidson EP, Dunlap JA, Lund DD, Salvemini D, and Yorek MA. Effect of M40403 treatment of diabetic rats on endoneurial blood flow, motor nerve conduction velocity and vascular function of epineurial ar-

terioles of the sciatic nerve. *Br J Pharmacol* 134: 21–29, 2001.
17. Coppey LJ, Gellett JS, Davidson EP, Dunlap JA, Lund DD, and Yorek MA. Effect of antioxidant treatment of streptozotocin-induced diabetic rats on endoneurial blood flow, motor nerve conduction velocity, and vascular reactivity of epineurial arterioles of the sciatic nerve. *Diabetes* 50: 1927–1937, 2001.
18. Cotter MA and Cameron NE. Effect of the NAD(P)H oxidase inhibitor, apocynin, on peripheral nerve perfusion and function in diabetic rats. *Life Sci* 73: 1813–1824, 2003.
19. Dekigai H, Murakami M, and Kita T. Mechanism of *Helicobacter pylori*-associated gastric mucosal injury. *Dig Dis Sci* 40: 1332–1339, 1995.
20. Ellis EA, Guberski DL, Hutson B, and Grant MB. Time course of NADH oxidase, inducible nitric oxide synthase and peroxynitrite in diabetic retinopathy in the BBZ/WOR rat. *Nitric Oxide* 6: 295–304, 2002.
21. El-Remessy AB, Abou-Mohamed G, Caldwell RW, and Caldwell RB. High glucose-induced tyrosine nitration in endothelial cells: role of eNOS uncoupling and aldose reductase activation. *Invest Ophthalmol Vis Sci* 44: 3135–3143, 2003.
22. Erdem A, Gundogan NU, Usubutun A, Kilinc K, Erdem SR, Kara A, and Bozkurt A. The protective effect of taurine against gentamicin-induced acute tubular necrosis in rats. *Nephrol Dial Transplant* 15: 1175–1182, 2000.
23. Fathallah L and Obrosova IG. Increased retinal lipid peroxidation in early diabetes is not associated with ascorbate depletion or changes in ascorbate redox state. *Exp Eye Res* 72: 719–723, 2001.
24. Geisen K, Utz R, Grotsch H, Lang HJ, and Nimmesgern H. Sorbitol-accumulating pyrimidine derivatives. *Arzneimittelforschung* 44: 1032–1043, 1994.
25. Giardino I, Fard AK, Hatchell DL, and Brownlee M. Aminoguanidine inhibits reactive oxygen species formation, lipid peroxidation, and oxidant-induced apoptosis. *Diabetes* 47: 1114–1120, 1998.
26. Greene DA, Arezzo JC, and Brown MB. Effect of aldose reductase inhibition on nerve conduction and morphometry in diabetic neuropathy. Zenarestat Study Group. *Neurology* 53: 580–591, 1999.
27. Gupta S, Chough E, Daley J, Oates P, Tornheim K, Ruderman NB, and Keaney JF Jr. Hyperglycemia increases endothelial superoxide that impairs smooth muscle cell Na^+-K^+-ATPase activity. *Am J Physiol Cell Physiol* 282: 560–566, 2002.
28. Ha HC, Hester LD, and Snyder SH. Poly(ADP-ribose) polymerase-1 dependence of stress-induced transcription factors and associated gene expression in glia. *Proc Natl Acad Sci U S A* 99: 3270–3275, 2002.
29. Hamada Y, Araki N, Horiuchi S, and Hotta N. Role of polyol pathway in nonenzymatic glycation. *Nephrol Dial Transplant* 11 (Suppl 5): 95–98, 1996.
30. Hamada Y, Nakamura J, Naruse K, Komori T, Kato K, Kasuya Y, Nagai R, Horiuchi S, and Hotta N. Epalrestat, an aldose reductase inhibitor, reduces the levels of Nε-(carboxymethyl)lysine protein adducts and their precursors in erythrocytes from diabetic patients. *Diabetes Care* 23: 1539–1544, 2000.
31. Heesom AE, Millward A, and Demaine AG. Susceptibility to diabetic neuropathy in patients with insulin dependent diabetes mellitus is associated with a polymorphism at the 5′ end of the aldose reductase gene. *J Neurol Neurosurg Psychiatry* 64: 213–216, 1998.
32. Herdener M, Heigold S, Saran M, and Bauer G. Target cell-derived superoxide anions cause efficiency and selectivity of intercellular induction of apoptosis. *Free Radic Biol Med* 29: 1260–1271, 2000.
33. Hermann M, Camici G, Fratton A, Hurlimann D, Tanner FC, Hellermann JP, Fiedler M, Thiery J, Neidhart M, Gay RE, Gay S, Luscher TF, and Ruschitzka F. Differential effects of selective cyclooxygenase-2 inhibitors on endothelial function in salt-induced hypertension. *Circulation* 108: 2308–2311, 2003.
34. Hodgkinson AD, Bartlett T, Oates PJ, Millward BA, and Demaine AG. The response of antioxidant genes to hyperglycemia is abnormal in patients with type 1 diabetes and diabetic nephropathy. *Diabetes* 52: 846–851, 2003.
35. Hoeldtke RD, Bryner KD, McNeill DR, Hobbs GR, Riggs JE, Warehime SS, Christie I, Ganser G, and Van Dyke K. Nitrosative stress, uric acid, and peripheral nerve function in early type 1 diabetes. *Diabetes* 51: 2817–2825, 2002.
36. Hotta N, Toyota T, Matsuoka K, Shigeta Y, Kikkawa R, Kaneko T, Takahashi A, Sugimura K, Koike Y, Ishii J, and Sakamoto N. SNK-860 Diabetic Neuropathy Study Group. Clinical efficacy of fidarestat, a novel aldose reductase inhibitor, for diabetic peripheral neuropathy: a 52-week multicenter placebo-controlled double-blind parallel group study. *Diabetes Care* 24: 1776–1782, 2001.
37. Hounsom L, Corder R, Patel J, and Tomlinson DR. Oxidative stress participates in the breakdown of neuronal phenotype in experimental diabetic neuropathy. *Diabetologia* 44: 424–428, 2001.
38. Inoguchi T, Li P, Umeda F, Yu HY, Kakimoto M, Imamura M, Aoki T, Etoh T, Hashimoto T, Naruse M, Sano H, Utsumi H, and Nawata H. High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C-dependent activation of NAD(P)H oxidase in cultured vascular cells. *Diabetes* 49: 1939–1945, 2000.
39. Ishii H, Tada H, and Isogai S. An aldose reductase inhibitor prevents glucose-induced increase in transforming growth factor-beta and protein kinase C activity in cultured mesangial cells. *Diabetologia* 41: 362–364, 1998.
40. Ito T, Nishimura C, Takahashi Y, Saito T, and Omori Y. The level of erythrocyte aldose reductase: a risk factor for diabetic neuropathy? *Diabetes Res Clin Pract* 36: 161–167, 1997.
41. Kador PF. The role of aldose reductase in the development of diabetic complications. *Med Res Rev* 8: 325–352, 1988.
42. Kamijo M, Basso M, Cherian PV, Hohman TC, and Sima AA. Galactosemia produces ARI-preventable nodal changes similar to those of diabetic neuropathy. *Diabetes Res Clin Pract* 25: 117–129, 1994.
43. Kato N, Yashima S, Suzuki T, Nakayama Y, and Jomori T. Long-term treatment with fidarestat suppresses the development of diabetic retinopathy in STZ-induced diabetic rats. *J Diabetes Complications* 17: 374–379, 2003.

44. Keogh RJ, Dunlop ME, and Larkins RG. Effect of inhibition of aldose reductase on glucose flux, diacylglycerol formation, protein kinase C, and phospholipase A2 activation. *Metabolism* 46: 41–47, 1997.
45. Kihara M, Schmelzer JD, Poduslo JF, Curran GL, Nickander KK, and Low PA. Aminoguanidine effects on nerve blood flow, vascular permeability, electrophysiology, and oxygen free radicals. *Proc Natl Acad Sci USA* 88: 6107–6111, 1991.
46. Kilic F, Bhardwaj R, Caufeild J, and Trevithick JR. Modelling cortical cataractogenesis 22: is in vitro reduction of damage in model diabetic rat cataract by taurine due to its antioxidant activity? *Exp Eye Res* 69: 291–300, 1999.
47. Kishi Y, Schmelzer JD, Yao JK, Zollman PJ, Nickander KK, Tritschler HJ, and Low PA. Alpha-lipoic acid: effect on glucose uptake, sorbitol pathway, and energy metabolism in experimental diabetic neuropathy. *Diabetes* 48: 2045–2051, 1999.
48. Kowluru RA, Engerman RL, and Kern TS. Abnormalities of retinal metabolism in diabetes or experimental galactosemia. VIII. Prevention by aminoguanidine. *Curr Eye Res* 21: 814–819, 2000.
49. Kubo E, Urakami T, Fatma N, Akagi Y, and Singh DP. Polyol pathway-dependent osmotic and oxidative stresses in aldose reductase-mediated apoptosis in human lens epithelial cells: role of AOP2. *Biochem Biophys Res Commun* 314: 1050–1056, 2004.
50. Lal S, Szwergold BS, Taylor AH, Randall WC, Kappler F, and Brown TR. Production of fructose and fructose-3-phosphate in maturing rat lenses. *Invest Ophthalmol Vis Sci* 36: 969–973, 1995.
51. Lee AYW and Chung SSM. Contribution of polyol pathway to oxidative stress in diabetic cataract. *FASEB J* 13: 23–30, 1999.
52. Lee SM, Schade SZ, and Doughty CC. Aldose reductase, NADPH and $NADP^+$ in normal, galactose-fed and diabetic rat lens. *Biochim Biophys Acta* 841: 247–253, 1985.
53. Li F, Szabo C, Pacher P, Southan GJ, Abatan OI, Charniauskaya T, Stevens MJ, and Obrosova IG. Evaluation of orally active poly(ADP-ribose) polymerase inhibitor in streptozotocin-diabetic rat model of early peripheral neuropathy. *Diabetologia* 47: 710–717, 2004.
54. Lim E, Park S, and Kim H. Effect of taurine supplementation on the lipid peroxide formation and the activities of glutathione-related enzymes in the liver and islet of type I and II diabetic model mice. *Adv Exp Med Biol* 442: 99–103, 1998.
55. Lindsay RM, Walker SA, McGuigan CC, Smith W, and Baird JD. Tissue ascorbic acid and polyol pathway metabolism in experimental diabetes. *Diabetologia* 41: 516–523, 1998.
56. Lou MF, Dickerson JE, Garadi R, and York BM Jr. Glutathione depletion in the lens of galactosemic and diabetic rats. *Exp Eye Res* 46: 517–530, 1988.
57. Lowitt S, Malone JI, Salem AF, Korthals J, and Benford S. Acetyl-L-carnitine corrects the altered peripheral nerve function of experimental diabetes. *Metabolism* 44: 677–680, 1995.
58. Mabley JG, Liaudet L, Pacher P, Southan GJ, Groves JT, Salzman AL, and Szabo C. Part II: beneficial effects of the peroxynitrite decomposition catalyst FP15 in murine models of arthritis and colitis. *Mol Med* 8: 581–590, 2002.
59. Maitra I, Serbinova E, Tritschler H, and Packer L. α–Lipoic acid prevents buthionine-sulfoximine-induced cataract formation in newborn rats. *Free Radic Biol Med* 18: 823–829, 1995.
60. Malone JI, Benford SA, and Malone J Jr. Taurine prevents galactose-induced cataracts. *J Diabetes Complications* 7: 44–48, 1993.
61. Matsumoto S, Koshiishi I, Inoguchi T, Nawata H, and Utsumi H. Confirmation of superoxide generation via xanthine oxidase in streptozotocin-induced diabetic mice. *Free Radic Res* 37: 767–772, 2003.
62. Mattson MP, Lovell MA, Furukawa K, and Markesbery WR. Neurotrophic factors attenuate glutamate-induced accumulation of peroxides, elevation of intracellular Ca^{2+} concentration, and neurotoxicity and increase antioxidant enzyme activities in hippocampal neurons. *J Neurochem* 65: 1740–1751, 1995.
63. Minchenko AG, Stevens MJ, White L, Abatan OI, Komjati K, Pacher P, Szabo C, and Obrosova IG. Diabetes-induced overexpression of endothelin-1 and endothelin receptors in the rat renal cortex is mediated via poly(ADP-ribose) polymerase activation. *FASEB J* 17: 1514–1516, 2003.
64. Myhre O and Fonnum F. The effect of aliphatic, naphthenic, and aromatic hydrocarbons on production of reactive oxygen species and reactive nitrogen species in rat brain synaptosome fraction: the involvement of calcium, nitric oxide synthase, mitochondria, and phospholipase A. *Biochem Pharmacol* 62: 119–128, 2001.
65. Nagamatsu M, Nickander KK, Schmelzer JD, Raya A, Wittrock DA, Tritschler H, and Low PA. Lipoic acid improves nerve blood flow, reduces oxidative stress, and improves distal nerve conduction in experimental diabetic neuropathy. *Diabetes Care* 18: 1160–1167, 1995.
66. Nagaraj RH, Prabhakaram M, Ortwerth BJ, and Monnier VM. Suppression of pentosidine formation in galactosemic rat lens by an inhibitor of aldose reductase. *Diabetes* 43: 580–586, 1994.
67. Nakamura J, Kato K, Hamada Y, Nakayama M, Chaya S, Nakashima E, Naruse K, Kasuya Y, Mizubayashi R, Miwa K, Yasuda Y, Kamiya H, Ienaga K, Sakakibara F, Koh N, and Hotta N. A protein kinase C-beta-selective inhibitor ameliorates neural dysfunction in streptozotocin-induced diabetic rats. *Diabetes* 48: 2090–2095, 1999.
68. Nakamura J, Kasuya Y, Hamada Y, Nakashima E, Naruse K, Yasuda Y, Kato K, and Hotta N. Glucose-induced hyperproliferation of cultured rat aortic smooth muscle cells through polyol pathway hyperactivity. *Diabetologia* 44: 480–487, 2001.
69. Niwa T. 3-Deoxyglucosone: metabolism, analysis, biological activity, and clinical implication. *J Chromatogr B Biomed Sci Appl* 731: 23–36, 1999.
70. Oates PJ and Mylari BL. Aldose reductase inhibitors: therapeutic implications for diabetic complications. *Expert Opin Investig Drugs* 8: 2095–2119, 1999.
71. Obrosova I, Faller A, Burgan J, Ostrow E, and Williamson JR. Glycolytic pathway, redox state of NAD(P)-couples and energy metabolism in lens in galactose-fed rats: effect of an aldose reductase inhibitor. *Curr Eye Res* 16: 34–43, 1997.

72. Obrosova IG. How does glucose generate oxidative stress in peripheral nerve? *Int Rev Neurobiol* 50: 3–35, 2002.
73. Obrosova IG. Update on the pathogenesis of diabetic neuropathy. *Curr Diab Rep* 3: 439–445, 2003.
74. Obrosova IG and Fathallah L. Evaluation of an aldose reductase inhibitor on lens metabolism, ATPases and antioxidative defense in streptozotocin-diabetic rats: an intervention study. *Diabetologia* 43: 1048–1055, 2000.
75. Obrosova IG and Stevens MJ. Effect of dietary taurine supplementation on GSH and NAD(P)-redox status, lipid peroxidation, and energy metabolism in diabetic precataractous lens. *Invest Ophthalmol Vis Sci* 40: 680–688, 1999.
76. Obrosova IG, Cao X, Greene DA, and Stevens MJ. Diabetes-induced changes in lens antioxidant status, glucose utilization and energy metabolism: effect of DL-α-lipoic acid. *Diabetologia* 41: 1442–1450, 1998.
77. Obrosova IG, Fathallah L, and Lang HJ. Interaction between osmotic and oxidative stress in diabetic precataractous lens: studies with a sorbitol dehydrogenase inhibitor. *Biochem Pharmacol* 58: 1945–1954, 1999.
78. Obrosova IG, Fathallah L, Lang HJ, and Greene DA. Evaluation of a sorbitol dehydrogenase inhibitor on diabetic peripheral nerve metabolism: a prevention study. *Diabetologia* 42: 1187–1194, 1999.
79. Obrosova IG, Greene DA, and Lang HJ. Antioxidative defense in diabetic peripheral nerve: effect of DL-α-lipoic acid, aldose reductase inhibitor and sorbitol dehydrogenase inhibitor. In: *Antioxidants in Diabetes Management,* edited by Packer L, Roesen P, Tritschler H, King G, and Azzi A. New York, NY: Marcel Dekker, 2000, pp. 93–110.
80. Obrosova IG, Fathallah L, and Stevens MJ. Taurine counteracts oxidative stress and nerve growth factor deficit in early experimental diabetic neuropathy. *Exp Neurol* 172: 211–219, 2001.
81. Obrosova IG, Minchenko AG, Marinescu V, Fathallah L, Kennedy A, Stockert CM, Frank RN, and Stevens MJ. Antioxidants attenuate early up regulation of retinal vascular endothelial growth factor in streptozotocin-diabetic rats. *Diabetologia* 44: 1102–1110, 2001.
82. Obrosova IG, Stevens MJ, and Lang HJ. Diabetes-induced changes in retinal NAD-redox status: pharmacological modulation and implications for pathogenesis of diabetic retinopathy. *Pharmacology* 62: 172–180, 2001.
83. Obrosova IG, Van Huysen C, Fathallah L, Cao XC, Greene DA, and Stevens MJ. An aldose reductase inhibitor reverses early diabetes-induced changes in peripheral nerve function, metabolism, and antioxidative defense. *FASEB J* 16: 123–125, 2002.
84. Obrosova IG, Fathallah L, Liu E, and Nourooz-Zadeh J. Early oxidative stress in the diabetic kidney: effect of DL-alpha-lipoic acid. *Free Radic Biol Med* 34: 186–195, 2003.
85. Obrosova IG, Minchenko AG, Vasupuram R, White L, Abatan OI, Kumagai AK, Frank RN, and Stevens MJ. Aldose reductase inhibitor fidarestat prevents retinal oxidative stress and vascular endothelial growth factor overexpression in streptozotocin-diabetic rats. *Diabetes* 52: 864–871, 2003.
86. Obrosova IG, Li F, Abatan OI, Forsell MA, Komjati K, Pacher P, Szabo C, and Stevens MJ. Role of poly(ADP-ribose) polymerase activation in diabetic neuropathy. *Diabetes* 53: 711–720, 2004.
87. Obrosova IG, Minchenko AG, Frank RN, Seigel GM, Zsengeller Z, Pacher P, Stevens MJ, and Szabo C. Poly(ADP-ribose) polymerase inhibitors counteract diabetes- and hypoxia-induced retinal vascular endothelail growth factor (VEGF) overexpression. *Int J Mol Med* 14: 55–64, 2004.
88. Obrosova IG, Pacher P, Szabo C, Zsengeller Z, Hirooka H, Stevens MJ, and Yorek MA. Aldose reductase inhibition counteracts oxidative-nitrosative stress and poly(ADP-ribose) polymerase activation in tissue sites for diabetes complications. *Diabetes* 54: 234–242, 2005.
89. Ou P and Wolff SP. Aminoguanidine: a drug proposed for prophylaxis in diabetes inhibits catalase and generates hydrogen peroxide in vitro. *Biochem Pharmacol* 46: 1139–1144, 1993.
90. Pacher P, Liaudet L, Soriano FG, Mabley JG, Szabo E, and Szabo C. The role of poly(ADP-ribose) polymerase activation in the development of myocardial and endothelial dysfunction in diabetes. *Diabetes* 51: 514–521, 2002.
91. Pacher P, Obrosova IG, Mabley JG, and Szabo C. Role of nitrosative stress and peroxynitrite in the pathogenesis of diabetic complications. Emerging new therapeutical strategies. *Curr Med Chem* 12:267–275, 2005.
92. Phillips SA, Mirrlees D, and Thornalley PJ. Modification of the glyoxalase system in streptozotocin-induced diabetic rats. Effect of the aldose reductase inhibitor Statil. *Biochem Pharmacol* 46: 805–811, 1993.
93. Pop-Busui R, Sullivan KA, Van Huysen C, Bayer L, Cao X, Towns R, and Stevens MJ. Depletion of taurine in experimental diabetic neuropathy: implications for nerve metabolic, vascular, and functional deficits. *Exp Neurol* 168: 259–272, 2001.
94. Purves T, Middlemas A, Agthong S, Jude EB, Boulton AJ, Fernyhough P, and Tomlinson DR. A role for mitogen-activated protein kinases in the etiology of diabetic neuropathy. *FASEB J* 15: 2508–2514, 2001.
95. Reckelhoff JF, Hennington BS, Kanji V, Racusen LC, Schmidt AM, Yan SD, Morrow J, Roberts LJ 2nd, and Salahudeen AK. Chronic aminoguanidine attenuates renal dysfunction and injury in aging rats. *Am J Hypertens* 12: 492–498, 1999.
96. Rittner HL, Hafner V, Klimiuk PA, Szweda LI, Goronzy JJ, and Weyand CM. Aldose reductase functions as a detoxification system for lipid peroxidation products in vasculitis. *J Clin Invest* 103: 1007–1013, 1999.
97. Robison WG Jr, Jacot JL, Glover JP, Basso MD, and Hohman TC. Diabetic-like retinopathy: early and late intervention therapies in galactose-fed rats. *Invest Ophthalmol Vis Sci* 39: 1933–1941, 1998.
98. Robison WG Jr, Jacot JL, Katz ML, and Glover JP. Retinal vascular changes induced by the oxidative stress of alpha-tocopherol deficiency contrasted with diabetic microangiopathy. *J Ocul Pharmacol Ther* 16: 109–120, 2000.
99. Saito H. Biochemical changes in lens, aqueous humor and vitreous body and effects of aldose reductase inhibitor (TAT) on rats with experimental diabetes. *Nippon Ika Daigaku Zasshi* 62: 339–350, 1995.

100. Shangari N, Bruce WR, Poon R, and O'Brien PJ. Toxicity of glyoxals—role of oxidative stress, metabolic detoxification and thiamine deficiency. *Biochem Soc Trans* 31: 1390–1393, 2003.
101. Siems WG, Grune T, and Esterbauer H. 4-Hydroxynonenal formation during ischemia and reperfusion of rat small intestine. *Life Sci* 57: 785–789, 1995.
102. Sone H, Kawakami Y, Okuda Y, Sekine Y, Honmura S, Matsuo K, Segawa T, Suzuki H, and Yamashita K. Ocular vascular endothelial growth factor levels in diabetic rats are elevated before observable retinal proliferative changes. *Diabetologia* 40: 726–730, 1997.
103. Song Z, Fu DT, Chan YS, Leung S, Chung SS, and Chung SK. Transgenic mice overexpressing aldose reductase in Schwann cells show more severe nerve conduction velocity deficit and oxidative stress under hyperglycemic stress. *Mol Cell Neurosci* 23: 638–647, 2003.
104. Srivastava S, Chandra A, Ansari NH, Srivastava SK, and Bhatnagar A. Identification of cardiac oxidoreductase(s) involved in the metabolism of the lipid peroxidation-derived aldehyde-4-hydroxynonenal. *Biochem J* 329: 469– 475, 1998.
105. Srivastava S, Chandra A, Wang LF, Seifert WE Jr, DaGue BB, Ansari NH, Srivastava SK, and Bhatnagar A. Metabolism of the lipid peroxidation product, 4-hydroxy-*trans*-2-nonenal, in isolated perfused rat heart. *J Biol Chem* 273: 10893–10900, 1998.
106. Stevens MJ, Hosaka Y, Masterson JA, Jones SM, Thomas TP, and Larkin DD. Downregulation of the human taurine transporter by glucose in cultured retinal pigment epithelial cells. *Am J Physiol* 277: E760–E771, 1999.
107. Stevens MJ, Obrosova IG, Cao X, Van Huysen C, and Greene DA. Effect of DL-α-lipoic acid on peripheral nerve conduction, blood flow, energy metabolism and oxidative stress in experimental diabetic neuropathy. *Diabetes* 49: 1006–1016, 2000.
108. Suarez G, Rajaram R, Oronsky AL, and Gawinowicz MA. Nonenzymatic glycation of bovine serum albumin by fructose (fructation). Comparison with the Maillard reaction initiated by glucose. *J Biol Chem* 264: 3674–3679, 1989.
109. Tomlinson DR, Stevens EJ, and Diemel LT. Aldose reductase inhibitors and their potential for the treatment of diabetic complications. *Trends Pharmacol Sci* 15: 293–297, 1994.
110. Trachtman H, Futterweit S, Maesaka J, Ma C, Valderrama E, Fuchs A, Tarectecan AA, Rao PS, Sturman JA, Boles TH, and Baynes J. Taurine ameliorates chronic streptozocin-induced diabetic nephropathy in rats. *Am J Physiol* 269: F429–F438, 1995.
111. Urata Y, Yamamoto H, Goto S, Tsushima H, Akazawa S, Yamashita S, Nagataki S, and Kondo T. Long exposure to high glucose concentration impairs the responsive expression of gamma-glutamylcysteine synthetase by interleukin-1beta and tumor necrosis factor-alpha in mouse endothelial cells. *J Biol Chem* 271: 15146–15152, 1996.
112. Virag L, Szabo E, Gergely P, and Szabo C. Peroxynitrite-induced cytotoxicity: mechanism and opportunities for intervention. *Toxicol Lett* 140–141: 113–124, 2003.
113. Williamson JR, Chang K, Frangos M, Hasan KS, Ido Y, Kawamura T, Nyengaard JR, van den Enden M, Kilo C, and Tilton RG. Hyperglycemic pseudohypoxia and diabetic complications. *Diabetes* 42: 801–813, 1993.
114. Yagihashi S, Yamagishi SI, Wada R, Baba M, Hohman TC, Yabe-Nishimura C, and Kokai Y. Neuropathy in diabetic mice overexpressing human aldose reductase and effects of aldose reductase inhibitor. *Brain* 124: 2448–2458, 2001.
115. Yamagishi S, Uehara K, Otsuki S, and Yagihashi S. Differential influence of increased polyol pathway on protein kinase C expressions between endoneurial and epineurial tissues in diabetic mice. *J Neurochem* 87: 497–507, 2003.
116. Yan SF, Ramasamy R, Naka Y, and Schmidt AM. Glycation, inflammation, and RAGE: a scaffold for the macrovascular complications of diabetes and beyond. *Circ Res* 93: 1159–1169, 2003.
117. Yeh LA and Ashton MA. The increase in lipid peroxidation in diabetic rat lens can be reversed by oral sorbinil. *Metabolism* 39: 619–622, 1990.
118. Zhang J, Schmidt J, Ryschich E, Mueller-Schilling M, Schumacher H, and Allenberg JR. Inducible nitric oxide synthase is present in human abdominal aortic aneurysm and promotes oxidative vascular injury. *J Vasc Surg* 38: 360–367, 2003.
119. Zingarelli B, Szabo C, and Salzman AL. Blockade of poly(ADP-ribose) synthetase inhibits neutrophil recruitment, oxidant generation, and mucosal injury in murine colitis. *Gastroenterology* 116: 335–345, 1999.
120. Zingarelli B, Hake PW, O'Connor M, Denenberg A, Kong S, and Aronow BJ. Absence of poly(ADP-ribose)polymerase-1 alters nuclear factor-kappa B activation and gene expression of apoptosis regulators after reperfusion injury. *Mol Med* 9: 143–153, 2003.

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2. Brian C Callaghan, Hsinlin T Cheng, Catherine L Stables, Andrea L Smith, Eva L Feldman. 2012. Diabetic neuropathy: clinical manifestations and current treatments. *The Lancet Neurology* **11**:6, 521-534. [CrossRef]
3. Çimen Karasu, Ahmet Cumao#lu, Ali Rifat Gúrpinar, Murat Kartal, Lucia Kovacikova, Ivana Milackova, Milan Stefek. 2012. Aldose reductase inhibitory activity and antioxidant capacity of pomegranate extracts. *Interdisciplinary Toxicology* **5**:1, 15-20. [CrossRef]
4. Andrea M. Vincent, Brian C. Callaghan, Andrea L. Smith, Eva L. Feldman. 2011. Diabetic neuropathy: cellular mechanisms as therapeutic targets. *Nature Reviews Neurology* . [CrossRef]
5. H. Liu, Y. Luo, T. Zhang, Y. Zhang, Q. Wu, L. Yuan, S. S. M. Chung, P. J. Oates, J. Y. Yang. 2011. Genetic deficiency of aldose reductase counteracts the development of diabetic nephropathy in C57BL/6 mice. *Diabetologia* **54**:5, 1242-1251. [CrossRef]
6. Irina G. Obrosova, Roman Stavniichuk, Viktor R. Drel, Hanna Shevalye, Igor Vareniuk, Jerry L. Nadler, Robert. E. Schmidt. 2010. Different Roles of 12/15-Lipoxygenase in Diabetic Large and Small Fiber Peripheral and Autonomic Neuropathies. *The American Journal of Pathology* **177**:3, 1436-1447. [CrossRef]
7. Iana Souza Nascimento, Eloísa Bonfá, Jozélio Freire de Carvalho, Carla Gonçalves Saad, Margarete Borges Galhardo Vendramini, Manoel Jacobsen Teixeira, José Cláudio Marinho Nóbrega, Vilma Santos Trindade Viana. 2010. Clues for Previously Undiagnosed Connective Tissue Disease in Patients With Trigeminal Neuralgia. *JCR: Journal of Clinical Rheumatology* **16**:5, 205-208. [CrossRef]
8. Irina G. Obrosova, Stephen S. M. Chung, Peter F. Kador. 2010. Diabetic cataracts: mechanisms and management. *Diabetes/Metabolism Research and Reviews* **26**:3, 172-180. [CrossRef]
9. Pierre Watcho, Roman Stavniichuk, David M. Ribnicky, Ilya Raskin, Irina G. Obrosova. 2010. High-Fat Diet-Induced Neuropathy of Prediabetes and Obesity: Effect of PMI-5011, an Ethanolic Extract of Artemisia dracunculus L. *Mediators of Inflammation* **2010**, 1-10. [CrossRef]
10. Tamara Kuchmerovska, Ihor Shymanskyy, Stefan Chlopicki, Arkady Klimenko. 2010. 1-Methylnicotinamide (MNA) in prevention of diabetes-associated brain disorders. *Neurochemistry International* **56**:2, 221-228. [CrossRef]
11. Qi Zhang, Guang-ji Wang, Ji-ye A, Di Wu, Ling-ling Zhu, Bo Ma, Yu Du. 2009. Application of GC/MS-based metabonomic profiling in studying the lipid-regulating effects of Ginkgo biloba extract on diet-induced hyperlipidemia in rats. *Acta Pharmacologica Sinica* **30**:12, 1674-1687. [CrossRef]
12. Todd W Burner, Ann K Rosenthal. 2009. Diabetes and rheumatic diseases. *Current Opinion in Rheumatology* **21**:1, 50-54. [CrossRef]
13. N. Da#-Evcimen, Ö. Yildirim, S. Suzen. 2009. Relationship between Aldose reductase and superoxide dismutase inhibition capacities of indole-based analogs of melatonin derivatives. *Archives of Biological Sciences* **61**:4, 675-681. [CrossRef]
14. Johan G. Olsen, Lise Pedersen, Christina L. Christensen, Ole Olsen, Anette Henriksen. 2008. Barley aldose reductase: Structure, cofactor binding, and substrate recognition in the aldo/keto reductase 4C family. *Proteins: Structure, Function, and Bioinformatics* **71**:3, 1572-1581. [CrossRef]
15. Milan Stefek, Vladimir Snirc, Paul-Omer Djoubissie, Magdalena Majekova, Vassilis Demopoulos, Lucia Rackova, Zelmira Bezakova, Cimen Karasu, Vincenzo Carbone, Ossama El-Kabbani. 2008. Carboxymethylated pyridoindole antioxidants as aldose reductase inhibitors: Synthesis, activity, partitioning, and molecular modeling. *Bioorganic & Medicinal Chemistry* **16**:9, 4908-4920. [CrossRef]
16. Pal Pacher. 2008. Poly(ADP-ribose) polymerase inhibition as a novel therapeutic approach against intraepidermal nerve fiber loss and neuropathic pain associated with advanced diabetic neuropathy: A commentary on “PARP Inhibition or gene deficiency counteracts intraepidermal nerve fiber loss and neuropathic pain in advanced diabetic neuropathy”. *Free Radical Biology and Medicine* **44**:6, 969-971. [CrossRef]
17. Maki Saito, Mayumi Ueo, Sokichi Kametaka, Orie Saigo, Seiichi Uchida, Hideo Hosaka, Kenji Sakamoto, Tsutomu Nakahara, Asami Mori, Kunio Ishii. 2008. Attenuation of Cataract Progression by A-3922, a Dihydrobenzofuran Derivative, in Streptozotocin-Induced Diabetic Rats. *Biological & Pharmaceutical Bulletin* **31**:10, 1959-1963. [CrossRef]
18. Ann M. Winter-Vann, Gary L. Johnson. 2007. Integrated activation of MAP3Ks balances cell fate in response to stress. *Journal of Cellular Biochemistry* **102**:4, 848-858. [CrossRef]

19. Jiang Fu, S. S. W. Tay, E. A. Ling, S. T. Dheen. 2007. Aldose reductase is implicated in high glucose-induced oxidative stress in mouse embryonic neural stem cells. *Journal of Neurochemistry* **103**:4, 1654-1665. [CrossRef]
20. S TAS, E SARANDOL, S AYVALIK, Z SERDAR, M DIRICAN. 2007. Vanadyl Sulfate, Taurine, and Combined Vanadyl Sulfate and Taurine Treatments in Diabetic Rats: Effects on the Oxidative and Antioxidative Systems. *Archives of Medical Research* **38**:3, 276-283. [CrossRef]
21. Dr. Melinda T. Coughlan , Mark E. Cooper , Josephine M. Forbes . 2007. Renal Microvascular Injury in Diabetes: RAGE and Redox Signaling. *Antioxidants & Redox Signaling* **9**:3, 331-342. [Abstract] [Full Text PDF] [Full Text PDF with Links]
22. Johannes Wohlrab, David Wohlrab, Frank Meiss. 2007. Skin diseases in diabetes mellitus. *JDDG* **5**:1, 37-53. [CrossRef]
23. Melinda T. Coughlan, Mark E. Cooper, Josephine M. Forbes. 2006. Renal Microvascular Injury in Diabetes: RAGE and Redox Signaling. *Antioxidants & Redox Signaling*, ahead of print061221112325002. [CrossRef]
24. Martin J. Stevens . 2005. Redox-Based Mechanisms in Diabetes. *Antioxidants & Redox Signaling* **7**:11-12, 1483-1485. [Citation] [Full Text PDF] [Full Text PDF with Links]