Aldose Reductase and Cardiovascular Diseases, Creating Human-Like Diabetic Complications in an Experimental Model

Ravichandran Ramasamy, Ira J. Goldberg

Abstract: Hyperglycemia and reduced insulin actions affect many biological processes. One theory is that aberrant metabolism of glucose via several pathways including the polyol pathway causes cellular toxicity. Aldose reductase (AR) is a multifunctional enzyme that reduces aldehydes. Under diabetic conditions AR converts glucose into sorbitol, which is then converted to fructose. This article reviews the biology and pathobiology of AR actions. AR expression varies considerably among species. In humans and rats, the higher level of AR expression is associated with toxicity. Flux via AR is increased by ischemia and its inhibition during ischemia reperfusion reduces injury. However, similar pharmacological effects are not observed in mice unless they express a human AR transgene. This is because mice have much lower levels of AR expression, probably insufficient to generate toxic byproducts. Human AR expression in LDL receptor knockout mice exacerbates vascular disease, but only under diabetic conditions. In contrast, a recent report suggests that genetic ablation of AR increased atherosclerosis and increased hydroxynonenal in arteries. It was hypothesized that AR knockout prevented reduction of toxic aldehydes. Like many in vivo effects found in genetically manipulated animals, interpretation requires the reproduction of human-like physiology. For AR, this will require tissue specific expression of AR in sites and at levels that approximate those in humans. (Circ Res. 2010;106:1449-1458.)

Key Words: diabetes ■ macrovascular disease ■ atherosclerosis ■ fructose
vascular disease (reviewed elsewhere) suggests that basic biological differences between humans and mice may alter the vasculotoxicity of diabetes.

Many genes are expressed in rodent tissues at levels that are disproportionate to those in humans, and these lead to changes in physiology and response to drugs that are totally different from those of humans. A case in point is the expression of peroxisome proliferator-activated receptor (PPAR) transcription factors. Rodent livers express much higher levels of both PPARα and PPARγ than do humans. For this reason, whereas activation of PPARα in rats led to marked proliferation of peroxisomes, a result that led to the vasculotoxicity of diabetes.

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In the case of diabetic complications, this might be most important. Efforts to replicate the pathology of diabetic nephropathy have been frustrating. Similarly, vascular disease, ischemia reperfusion injury that is a surrogate for myocardial infarction, and cardiomyopathies associated with diabetes using rodent models have used genetic modifications that allow similar end points as found in humans; although many of the phenotypes are accelerated suggesting that the effects are either pharmacological or represent extremes. Similarly, although genetic deletions can sometimes unmask effects are either pharmacological or represent extremes. Many genes are expressed in rodent tissues at levels that are disproportionate to those in humans, and these lead to changes in physiology and response to drugs that are totally different from those of humans. A case in point is the expression of peroxisome proliferator-activated receptor (PPAR) transcription factors. Rodent livers express much higher levels of both PPARα and PPARγ than do humans. For this reason, whereas activation of PPARα in rats led to marked proliferation of peroxisomes, a result that led to the vasculotoxicity of diabetes.

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**Hyperglycemia in Myocardial Cells**

Chronic hyperglycemia exerts its damaging effects on cardiovascular tissue by multiple mechanisms. Nonenzymatic glycation reactions of extracellular molecular species and advanced glycation end products (AGEs), which result from spontaneous chemical rearrangements of glycation products, are one mechanism by which hyperglycemia exerts its damaging effects. These derivatives can bind to preexisting glyated protein or AGE cell surface receptors. The interactions of such ligands with cell surface membrane receptors can lead to generation of reactive oxygen species.

Intracellular effects of chronic hyperglycemia are linked to the key observation that cardiovascular tissue is at least partly independent of insulin for uptake of glucose from the extracellular environment. However, in the presence of chronic hyperglycemia, there is an inadequate downregulation of the non–insulin-dependent transporters and the cells are consequently subjected to continuous influx of abnormally high amounts of glucose into their cytosol. Chronic elevation of cytosolic glucose levels and/or metabolic flux is associated with generation of excess intracellular superoxide and other mediators of oxidative stress, an insult now generally acknowledged to play an important role in the pathogenesis of diabetic complications.

Chronic elevation of glucose alters the biochemical homeostasis of cardiovascular cells by impacting a number of key biochemical pathways - including the polyl pathway, the cytoplasmic redox state, the protein kinase (PK)C pathway, and the glucoseamine biosynthesis pathway - and production of intracellular glycat ing species. In some cell types such as cultured bovine aortic endothelial cells, chronic hyperglycemia causes enhanced glycolytic and mitochondrial oxidative metabolism. In other cell types, such as in rat cardiac tissue, chronic hyperglycemia inhibits glycolytic rates and alters substrate use of cardiovascular cells. The primary emphasis in this review will be on AR, the first enzyme of the polyl pathway, which sits high in the biochemical cascade that follows the entry of excess glucose into the cytosol of cardiovascular cells.

**Characteristics of AR Activity**

AR (EC no. 1.1.1.21; AKR1B1, ALD2) is a member of the aldo-keto reductase superfamily and has been extensively studied. It is a monomeric, cytoplasmic enzyme of 35,900 Daltons with a triose phosphate isomerase structural motif that contains 10 peripheral α-helical segments surrounding an inner barrel of βpleated sheet segments. The enzyme preferentially and reversibly binds NADPH in an extended conformation and uses the hydrate of the C4 of the nicotinamide ring of NADPH to reduce an aldehydic molecule to the corresponding alcohol, eg, straight-chain aldehydic glucose to sorbitol. AR lacks structural carbohydrate and no catalytic or structural metal ion has been detected. As originally shown by Hers, AR reduces a variety of aldehydic substrates with varying affinities. However, its "natural" substrate remains elusive. Human AR efficiently uses 4-hydroxynonenal (4-HNE), 2-methylpentanal, glyceraldehyde, retinoids, and methylglyoxal, with Km values in the 8 to 50 μmol/L range. Most studies allude to Km for glucose in millimolar range. However, these studies often ignore key properties of glucose. Inagaki et al investigated the glucose anomer specificity of AR and calculated that AR acts on the aldohexide form of α-glucose with a Km of 0.66 μmol/L, ie, it is a higher affinity substrate than many others.
The AR catalytic center contains a key cysteine residue, Cys298, which when oxidized causes AR to exhibit altered properties and inhibitor sensitivity. The enzyme was recently reported to be catalytically altered by S-nitrosothiols, activated by nitric oxide under ischemic conditions in non-diabetic heart, and inhibited by exposure of diabetic rat brain, heart, and nerve to elevated nitric oxide levels. In human tissues AR has primarily a single, reduced enzyme form. There is wide interindividual variability of AR levels in a particular tissue, likely because of genetic allelic differences.

Polymorphisms of ALD2 and Risk of Diabetic Complication

The human AR gene (ALD2 or AKR1B1) is on locus q35 of human chromosome 7. ALD2 is approximately 18 kb and includes 10 exons coding for 316 amino acids. The ALD2 promoter has a TATA box (at −37), a CCAAT box (−104), and an androgen-like response element (−396 to −382). At approximately 1200 bp upstream of the transcription start site, there is a 132-bp region containing 3 osmotic response elements: OreA, OreB, and OreC. ALD2 pseudogenes have also been described.

Genetic polymorphisms associated with the human ALD2 gene have been linked to diabetic complications. The first reported microsatellite polymorphism was an (AC)n repeat region located ∼2.1 kb upstream of the transcription start site. Two single nucleotide polymorphisms (SNP) have been detected in the basal promoter region of the ALD2 gene, C(−106)T51 and C(−129)G52. In addition, a BamHI site consisting of an A to C substitution was reported at the 95th nucleotide of intron 8. The (AC)n and C(−106)T polymorphisms are closely linked, but their effects may be distinguishable in different patient populations. The “Z-2” (AC)n microsatellite polymorphism, ie, (AC)23 has been associated with high expression levels of AR56 and with rapid progression or increased prevalence of diabetic retinopathy,50,54 diabetic nephropathy, and, less strongly, with progression or increased prevalence of diabetic retinopathy.58 In the last case, a relatively clear association was detected between microvascular complications and a decrease in the “protective,” low AR-expressing genotype; they have normal structural, biochemical, reproductive and physiological properties. Consistent with the known osmoregulatory function of AR, their only abnormality is mild polyuria compensated by mild polydipsia. Urine and blood divalent cation concentration was also slightly altered, but it remains unclear if the changes were secondary to mild chronic diuresis or if AR plays a role in maintaining systemic divalent cation levels. Other processes that lead to generalized increases in oxidant stress are associated with aging. This is not found in these mice. In part, this might be because the relatively low AR expression in the mouse has

Physiological Functions of AR

Despite decades of experimental studies and the creation of genetically modified mice, the physiological function of AR is poorly defined. Originally discovered in seminal vesicles, the polyol pathway was hypothesized to be a biosynthetic route for producing fructose for the energy needs of spermatozoa. In the inner medulla of the kidney, AR synthesis of intracellular sorbitol may help protect cells from the locally high osmotic forces associated with antidiuresis. Perhaps for this reason, pharmacological suppression of AR activity upregulates other components of the renal osmolyte system to compensate for the loss of sorbitol. Genetic deletion of AR in mice also supports a role for AR in normal kidney function and, as noted above, shows that at least in kidney AR expression is regulated by expression of other genes in the renal medulla.

AR activity alters metabolism of glucose and produces a number of downstream carbohydrates. These include sorbitol-6-phosphate, sorbitol-3-phosphate, and fructose-3-phosphate, formed in part via the polyol pathway activity; the physiological roles of these molecules is unknown. AR has been proposed to function as a “fuel switch,” diverting excess glucose away from energy metabolism. It may metabolize steroids and catecholamines, and detoxify aldehydes, or their glutathionylated derivatives. Because the broad substrate specificity of AR overlaps with that of ubiquitous, structurally related enzymes like aldehyde reductase and aldehyde dehydrogenase, it is difficult to define the role of AR simply on the basis of substrate preference.

AR is proposed to also function as an antioxidant defense enzyme. Such actions need to be carefully analyzed and interpreted because many in vivo antioxidant defense pathways exert cytotoxic properties. Overexpression of AR in vivo has been linked to increased, rather than decreased, oxidative stress. In addition, in cultured endothelial cells exposed to hyperglycemia, as well as in diabetic and galactosemic peripheral nerve and retina in vivo, structurally distinct AR inhibitors (ARIs) suppress and reverse (and do not accentuate) markers of aldehydic and oxidative stress. These results appear to contrast with total deletion of the AR gene.

Adding to the AR functional conundrum are data from AR “knockout” mice. Despite the fact that AR is absent from all tissues, these genetically-engineered mice have minimal phenotype; they have normal structural, biochemical, reproductive and physiological properties. Consistent with the known osmoregulatory function of AR, their only abnormality is mild polyuria compensated by mild polydipsia. Urine and blood divalent cation concentration was also slightly altered, but it remains unclear if the changes were secondary to mild chronic diuresis or if AR plays a role in maintaining systemic divalent cation levels. Other processes that lead to generalized increases in oxidant stress are associated with aging. This is not found in these mice. In part, this might be because the relatively low AR expression in the mouse has

Expression of AR in Tissues

AR is widely distributed in many tissues. In humans, AR immunoreactivity is most concentrated in the inner medulla of kidney, and is abundant in human sciatic nerve, lung, small intestine, and colon. Unlike rats, mice have much lower levels of AR expression and activity than humans. A recent report suggests that in mice, AR protein expression is especially robust in vascular endothelial cells and within macrophages of atherosclerotic lesions.
been proposed.90 There are a number of interactions of the polyol pathway independent of osmotic stress has complications.

Figure 1. Flow diagram illustrating the interplay between polyol pathway, glycolysis, AGE precursor generation, and diacylglycerol (activator of PKC) generation. It is important to note that arrows are drawn to show competition between SDH and GAPDH for cytosolic NADH, thus impacting glycolysis.

Polyol Pathway: Prevailing Hypothesis and Mechanisms in Diabetes

To understand the potential role of AR in mediating diabetic cardiovascular complications, an overview of prevailing hypotheses and proposed mechanisms are essential. The “Osmotic Hypothesis” is that high levels of glucose are metabolized through AR and sorbitol dehydrogenase (SDH) to generate high intracellular levels of polyhydroxylated sorbitol and fructose (polyls). The polyol pathway for aberrant glucose metabolism has been viewed as a potential cause of several diabetic complications (Figure 1). First described almost 50 years ago,67 the pathway is comprised of 2 oxidoreductases, AR and SDH. In the presence of coenzyme reductase competed for the same pool of cytoplasmic NADPH. Williamson and colleagues demonstrated a strong linkage between polyol pathway flux and the ratio of free cytosolic NADH to NAD⁺, a factor critical to vascular function.92,93 Excess flux of glucose through AR impacts a variety of important metabolic pathways such as glycolysis, oxidative stress, intracellular nonenzymatic glycation and PKC activation.8,17,20,22,23,25

Diabetes-Induced Cardiovascular Disease in the Mouse

One of the burning questions in AR biology relates to its role in diabetic vascular disease. Because mice do not normally develop atherosclerosis, they require genetic manipulation to produce the hypercholesterolemia that is the essential ingredient in atherosclerosis. Although the plasma cholesterol levels are often at extremes that rarely occur in humans, this allows atherosclerosis within an acceptable timetable. However, extremely high cholesterol levels will “swamp out” many modifying effects that are seen when the hyperlipidemic causes of disease are less intense. An additional issue with the usual methods of studying atherosclerosis in mice is the use of juvenile animals. A recent report showed that older mice, more representative of middle-aged humans who develop atherosclerosis, develop more inflammation and disease when placed on an atherogenic diet.94

Another extreme condition is the method to create diabetes. The most common technique is the destruction of islet cells using streptozotocin. This creates severe insulin deficiency, but also can lead to marked hypercholesterolemia in genetically modified mice.95 In contrast, diets lead to more mild phenotypes. Genetic modifications such as loss of leptin signaling lead to hyperglycemia and hyperlipidemia, but are associated with defects in lymphocytes that actually reduce atherosclerosis.96

There are a number of pathways of aberrant glucose metabolism that are postulated to lead to vascular toxicity. Although deflection of glucose into any of these pathways could exacerbate toxicity, AR is an enzyme that is expressed at extremely low levels in the mouse (Figure 2).97 In an effort to determine whether AR deficiency was responsible, in part, for the failure of many mouse models to accelerate atherosclerosis with diabetes a transgenic mouse line was created in which human (h)AR was expressed via a histocompatibility gene promoter, leading to generalized AR overexpression.98 This transgene led to enzyme levels that were not dissimilar to those in humans. The mice have no obvious phenotype. When crossed onto the atherogenic LDL receptor knockout background, the hAR transgene had no effect on atherosclerosis in nondiabetic mice.97 However, in streptozotocin-induced diabetic mice, the transgene accelerated disease. This was associated with evidence of alteration in the glutathione antioxidant system. In contrast, expression of hAR in high fat diet-fed mice with mild insulin resistance without hyperglycemia had no effect on vascular lesions.99 Thus, it appears that hyperglycemia is needed and might need to be sufficiently increased to provide substrate for AR. In contrast, in the presence of higher cholesterol levels, AR effects were “swamped,”100 and AR inhibitors (ARIs) also did not alter
lesion extent. Others have found increased AR expression in activated macrophages and suggested that this enzyme is inflammatory because AR inhibition led to reduced oxidative stress.\textsuperscript{101,102}

In contrast, a recent study in apolipoprotein E knockout mice found increased early lesion size in control and diabetic mice in the AR knockout mice and greater lesion progression with ARI treatment.\textsuperscript{64} Lesion size was correlated with the presence of 4-HNE, which the authors postulated was attributable to defective removal of toxic phospholipid aldehydes. Surprisingly, the larger lesions were also associated with more collagen, a marker of greater lesion stability. The differences in the studies of AR transgenics and knockouts are reminiscent of those with alterations of endothelial nitric oxide synthase in which knockout and overexpression are both associated with greater lesion formation, and lead to the following questions: Is knockout associated with compensatory regulation, including upregulation of other genes that alter vascular biology? Is genetic overexpression a pharmacological effect or a reproduction of human pathophysiology? Furthermore, emerging studies on the impact of aldehyde dehydrogenase-2 (ALDH-2) in detoxifying 4-HNE\textsuperscript{103} adds further complexity to interpretation of lipotoxic aldehyde levels in AR overexpressing and AR knockout mice. Clearly, comprehensive investigations on the interplay between AR and ALDH-2 in detoxifying 4-HNE and other lipotoxic aldehydes in hAR and AR knockout mice is critical to resolving these contrasting findings.

**AR and Vascular Injury**

AR is implicated in excess smooth muscle cell (SMC) growth; a model of vascular repair. AR inhibition prevents SMC growth in culture and in situ in balloon-injured carotid arteries\textsuperscript{104–109} Inhibiting the increased glucose flux via the AR pathway attenuated high-glucose-induced diacylglycerol accumulation and PKC activation in SMCs.\textsuperscript{105} Prevented high-glucose-induced stimulation of the extracellular signal–related kinase/mitogen-activated protein kinase and phosphatidylinositol 3-kinase,\textsuperscript{106} activated nuclear factor \( \kappa B \),\textsuperscript{107} and decreased SMC chemotaxis, vascular inflammation, and adhesion. These data provide a rationale for evaluation of ARIs in diabetic patients undergoing angioplasty.

**AR and the Heart**

Glucose flux via AR increases under ischemic conditions, even in the absence of diabetes.\textsuperscript{25,41,63,86,87} The effects of the polyol pathway on ischemia/reperfusion (I/R) injury have been demonstrated in multiple studies using ex vivo isolated perfused hearts and in vivo transient occlusion and reperfusion of the left anterior descending coronary artery in mice and rats.\textsuperscript{41,63,110,111} In such studies, inhibition of AR reduced ischemic injury and was associated with attenuation of the rise in cytosolic redox (NADH/NAD+ ratio), improved glycolysis, increased ATP levels, and maintained normal sodium and calcium ion homeostasis in the heart post-I/R.\textsuperscript{41,63,110,111}

Transgenic mice expressing human-relevant levels of AR demonstrated more heart injury after I/R than wild-type mice.\textsuperscript{63} Consistent with the premise that injury was increased directly via AR, inhibitors of AR in these transgenic mice reduced I/R injury.\textsuperscript{63} Importantly, mice expressing human AR had several fold greater activity than wild-type mice and the amounts of human AR expressed in these transgenic mice were similar to those seen in humans.\textsuperscript{63}

Studies addressing mechanisms by which AR influences cardiac I/R injury have demonstrated key roles for this pathway in opening the mitochondrial permeability transition pore (MPTP).\textsuperscript{111} Compared to wild-type hearts, AR transgenic hearts had higher MPTP opening, increased generation of hydrogen peroxide, and reduced levels of antioxidant glutathione.\textsuperscript{111} Antioxidants or ARIs significantly reduced generation of reactive oxygen species and inhibited MPTP opening in AR transgenic mitochondria after I/R.\textsuperscript{111} Taken together, these studies implicate the AR pathway as a key player in mediating I/R injury in the heart.

In rabbit hearts inhibition of AR was protective,\textsuperscript{112} although it has also been reported to abolish the cardioprotective effects of ischemic preconditioning.\textsuperscript{113} Although others\textsuperscript{114} showed increases in AR activity during ischemia consistent with our earlier publication,\textsuperscript{41} they were unable to demonstrate cardioprotection with ARIs in a glucose perfused isolated rat heart I/R model. Reasons for these contrasting findings are not clear but may be attributable to model-dependent variations and substrate availability.

AR has been proposed to also detoxify aldehydes such as 4-HNE that accumulate during I/R. However, Chen et al demonstrated that activation of ALDH2 reduces 4-HNE accumulation and protects hearts from ischemic damage.\textsuperscript{103} We\textsuperscript{63} and Iwata et al\textsuperscript{115} have demonstrated that AR overexpressing mouse hearts exhibit increased injury and poor functional recovery after myocardial I/R, and have changes associated with increased oxidative stress. Furthermore, mice expressing human AR had greater injury and greater malondialdehyde content than wild-type mice with lower AR activity.\textsuperscript{63} In contrast, AR-null mice were reported to have reduced oxidative stress and protection against ischemic injury.\textsuperscript{116} In rat hearts subjected to I/R, increases in polyol...
pathway activity exacerbate oxidative damage. Furthermore, AR inhibition in animals does not cause increases in lipid peroxidation products such as malonyldialdehyde. Comprehensive measurements of 4-HNE and the role of ALDH2 will help resolve the role of AR as detoxifying enzyme in ischemic hearts.

Changes in AR expression have been demonstrated in diabetic and failing hearts. In Type 2 diabetic rat hearts, increased substrate flux via AR and SDH was observed in acute diabetics and in chronic diabetics both increases in expression of AR and SDH and greater flux via these enzymes was observed. In dogs, AR expression was attenuated in pacing induced heart failure. In humans, greater than 1.7-fold increases in AR expression were observed in patients with ischemic cardiomyopathy and diabetic cardiomyopathy. These important data underscore the importance of addressing the role of AR using rodent models of heart failure.

Clinical Applications of ARIs in Humans

Experimental evidence in rodents supports the benefits of AR inhibition in the diabetic cardiovascular tissue (Figure 3). Two classes of AR inhibitors have been extensively tested, the carboxylic acid class and the hydantoins, although novel classes of ARIs are in development. In a study by Johnson et al, diabetic subjects (with neuropathy) treated with zopolrestat for 1 year displayed increased left ventricular ejection fraction (LVEF), cardiac output, left ventricle stroke volume and exercise LVEF. In contrast, placebo-treated subjects demonstrated decreased exercise cardiac output, stroke volume and end diastolic volume. In another clinical study, ARI treatment was associated with improved autonomic variability in diabetic patients with autonomic neuropathy. These relatively small but key studies in human subjects with established diabetic complications underscore the promising potential of inhibiting AR in the heart in long-term diabetes.

Inhibitors of AR have been extensively studied in animal models of diabetes, both classes of ARIs show protective effects; they reduced albuminuria, mesangial expansion, and thickening of the glomerular basement membrane. Genetic modulation of AR alters development of nephropathy. Galactose fed AR transgenic mice developed pathological changes in the kidney consistent with nephropathy. In other studies, AR activity and transforming growth factor-β1 and type IV collagen mRNA levels were significantly increased in glomeruli from transgenic mice (versus wild-type mice) exposed to AGE-BSA, in a manner suppressed by the ARI zopolrestat. Mesangial cells cultured from AR transgenic mice exposed to AGE-BSA demonstrated greater increases in AR activity, and transforming growth factor-β1 and type IV collagen mRNA and protein versus wild-type cells. These increases were suppressed by either zopolrestat or AR antisense oligonucleotides.

Positive proof-of-concept studies in diabetic patients with nephropathy treated with ARIs have been reported. Administration of tolrestat to type 1 diabetic subjects for a 6-month period reduced urinary albumin excretion. Administration of epalrestat to type 2 diabetic subjects for 5 years prevented increases in urinary albumin excretion rates. In other studies, zopolrestat was administered to normotensive type 1 diabetic subjects for 1 year. After 3 months of treatment, zopolrestat administration caused a 34% reduction in urinary albumin excretion that was not correlated with changes in glycosylated hemoglobin or blood pressure; this effect persisted through 6, 9, and 12 month time periods. Taken together, these data strongly suggest that AR promotes diabetic cardiovascular and renal complications. A large randomized multicenter human trial using an ARI that is relatively free from skin and liver side effects will help establish its therapeutic potential in diabetic cardiovascular and renal complications.

Summary

AR is a central enzyme in the polyol pathway implicated in aberrant glucose metabolism and diabetic complications. We
have proposed a working model based on the comprehensive analysis of the data on AR in diabetic complications. Although there are ongoing studies of ARIs in humans, additional animal data are required to determine the role(s) of this enzyme under normal and pathological conditions. Both inhibitor studies and knockout mice at test to the relatively benign nature of AR loss. Indeed, the relatively low expression of this enzyme in control mice suggests that AR inhibition, unless total, is not likely to be toxic and is likely to be protective during hyperglycemia. Recent studies in AR knockout mice do suggest that caution is warranted. How best to examine the physiological actions of AR in humans is open to debate. However, best efforts to reproduce AR human biology in experimental animals are needed to mimic the conditions representing human disease.

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Disclosures

None.

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