AKR1B10 is induced by hyperglycaemia and lipopolysaccharide in patients with diabetic nephropathy

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Abstract Aldose reductase family member B10 (AKR1B10) belongs to the aldo-keto reductase gene superfamily and is closely related to aldose reductase (AKR1B1). It has been shown that AKR1B10 is present in many of the same human tissues as AKR1B1. The objective of this study was to investigate whether AKR1B10 has a role in diabetic nephropathy (DN) by investigating its response to high glucose and inflammation, both of which have been associated with the development and progression of DN. Expression levels of AKR1B10 were determined in peripheral blood mononuclear cells (PBMCs) obtained from 25 patients with type 1 diabetes and nephropathy, 25 without DN and 25 normal healthy controls that were exposed to high glucose (25 mM D-glucose) and also the inflammatory stressor lipopolysaccharide (LPS, 10 μ m). Under high glucose and LPS conditions, there was a significant increase in the expression of AKR1B10 in the PBMCs from patients with DN compared to those without DN and the normal controls. In conclusion, these results suggest that AKR1B10 may have an important role in the development and progression of DN.

Keywords Aldose reductase family member B10 · Aldose reductase · Diabetic nephropathy · High glucose · Inflammation · Type 1 diabetes

Introduction

Diabetic nephropathy is a leading cause of end-stage renal disease (ERSD) (Ritz et al. 1999; Adler et al. 2003). In both

type 1 and type 2 diabetes, approximately 50 % of patients develop microalbuminuria, and of these, 20–30 % goes on to develop proteinuria and, eventually, ERSD (Marshall 2004). Hyperglycaemia is considered to be a major causative factor in the development of long-term diabetic complications including diabetic nephropathy (DN) (DCCTRG 1993). It has been shown that an increased flux through the polyol pathway due to high glucose is linked to abnormalities such as osmotic and oxidative stress, which have been cited as promoters of diabetic microvascular disease (Brownlee 2005). Aldose reductase (AKR1B1) is the rate-limiting enzyme of the polyol pathway; we and others have shown that an increase in the activity of this enzyme contributes to the development and progression of DN (Srivastava et al. 2005; Chung and Chung 2001; Hodgkinson et al. 2001; Demaine 2003).

Studies have shown that some human tissues contain AKR1B1 as well as aldose reductase family 1 member B10 (AKR1B10), a closely related member of the same gene family (Hyndman and Flynn 1998; Huang et al. 2010). Although the exact biological role of AKR1B10 remains unclear, it has been implicated in a number of metabolic pathways in the cell including retinoic acid synthesis (Gallego et al. 2006). Retinoic acid is synthesised by series of oxidation steps, from retinol to retinaldehyde to retinoic acid (Napoli 1999). Members of three families of oxidoreductase enzymes have been implicated in retinol metabolism, alcohol dehydrogenase enzymes, short-chain dehydrogenases/reductases and aldo-keto reductases. Gallego et al. (2006) conducted a comparative analysis of ADH1B2, ADH4, RDH4, RDH11, AKR1B1 and AKR1B10, to determine their catalytic efficiency for the oxidation of retinol to retinaldehyde and the reduction of retinaldehyde to retinol. Their data suggest that while the alcohol dehydrogenases are effective retinol dehydrogenases, oxidising retinol to retinaldehyde, RDH11 and AKR1B10 are both effective retinaldehyde reductases, working in the opposite direction to reduce retinaldehyde to retinol. While the oxidation

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of retinol to retinaldehyde is reversible, the oxidation of retinaldehyde to retinoic acid is not; therefore, the cellular concentration of retinaldehyde and, thus, its generation is a direct determinate of retinoic acid levels. This suggests that if AKR1B10 is acting as a retinaldehyde reductase *in vivo*, then, it may play a role in retinoic acid homeostasis. Evidence from cell lines suggests that AKR1B10 reduces both all-*trans*-retinaldehyde and 9-*cis*-retinaldehyde, reducing their availability for retinoic acid synthesis (Ruiz et al. 2009). HeLa cells were transfected with a retinoic acid reporter plasmid and then either with an AKR1B10-expressing plasmid or a lacZ plasmid as a control. While the cells were responsive to treatment with all-*trans*-retinoic acid, the cells over-expressing AKR1B10 had a significantly reduced response to all-*trans*-retinol in comparison to the lacZ control cells. This suggests that over-expression of AKR1B10 in disease states may have the downstream effect of reducing cellular retinoic acid levels.

Retinoic acid is a key intercellular signalling molecule during vertebrate embryogenesis (Duester 2008), initially organising the development of the trunk. In the developed vertebrate, retinoic acid signalling has been linked with the inflammatory response, having been demonstrated to down-regulate both nuclear factor kappa B (NF- κ B) and activator protein-1 (AP-1) via the RXR (Na et al. 1999; Simonson 1994). The pathogenesis of diabetic nephropathy involves a number of factors including hyperglycaemia-induced oxidative stress and inflammation. Evidence from patients with diabetic nephropathy, including an up-regulation of monocyte chemotactic protein-1 (MCP-1), a chemoattractant molecule that recruits monocytes and macrophages (Boring et al. 1997; Tesch 2008), and from animal models, including an increase in macrophage infiltration in the kidney (Sassy-Prigent et al. 2000), supports the role of inflammation in the development of diabetic nephropathy. Given that the inflammatory response has been demonstrated to play a key role in the aetiology of diabetic nephropathy and that an increase in the availability of retinoic acid can down-regulate pro-inflammatory signalling pathways, it seems sensible that retinoic acid may protect against renal damage in diabetes. Evidence from both animal and cell line models of diabetic nephropathy supports this notion. In a rat model of diabetic nephropathy, treatment with retinoic acid improved both urinary protein excretion and albumin/creatinine ratio; additionally, retinoic acid treatment reduced MCP-1 expression by 30 %. Cell line research has indicated that MCP-1 is expressed by podocytes, and in cultured podocytes, MCP-1 is unregulated by high glucose, and this response is attenuated by retinoic acid (Han et al. 2004).

To our knowledge, there has been no study investigating the role of AKR1B10 in patients with type 1 diabetes mellitus and nephropathy. Therefore, the aim of this study was to investigate the expression levels of AKR1B10 in response to the cellular stressors, high glucose (HG), and the inflammatory stimulator lipopolysaccharide (LPS) in peripheral blood

mononuclear cells from the patients with type 1 diabetes and with or without nephropathy and normal healthy controls.

Materials and methods

Subjects

Fifty Caucasoid individuals with type 1 diabetes (T1D), as defined by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2003) were recruited from the Diabetic Out-patient Clinic, Derriford Hospital. Normal healthy control subjects ($n=25$) were ethnically matched to Caucasoid volunteers with no family history of diabetes. The study was approved by the local research ethical committee, and informed consent was obtained from all the subjects.

The patients were classified according to their microvascular complications as previously described (Heesom et al. 1997).

Uncomplicated patients ($n=25$) These individuals have been diagnosed with type 1 diabetes mellitus (T1DM) for at least 20 years but remain free of retinopathy (fewer than five dots or blots per fundus) and proteinuria (Albustix-negative urine on three consecutive occasions over 12 months). Overt neuropathy was defined as if there was any clinical evidence of peripheral or autonomic neuropathy.

Patients with nephropathy (nephropaths) ($n=25$) These individuals have had T1DM for at least 10 years with persistent proteinuria (urine Albustix on at least three consecutive occasions over 12 months or three consecutive total urinary protein excretion rates of >0.5 g/24 h) in the absence of haematuria or infection on midstream urine samples. Diabetic nephropathy was always associated with retinopathy. Retinopathy was defined as more than five dots or blots per eye; hard or soft exudates, new vessels, or fluorescein angiographic evidence of maculopathy or previous laser treatment for preproliferative or proliferative retinopathy; and maculopathy or vitreous haemorrhage. Fundoscopy was performed by both a diabetologist and an ophthalmologist. The clinical characteristics of the subjects are shown in Table 1.

Healthy control subjects ($n=25$) Peripheral blood samples were obtained from the healthy volunteers with no family history of type 1 or type 2 diabetes.

Cell isolation and cultures

Peripheral venous blood samples (20 ml) were collected into vacutainers (Becton Dickinson, Oxford, UK), and the peripheral blood mononuclear cells (PBMCs) were separated using Histopaque (Sigma, UK). PBMCs were washed and resuspended at a concentration of 0.5×10^6 /ml in RPMI 1640 (no

Table 1 Clinical characteristics of patients with type 1 diabetes mellitus and normal healthy controls

	Diabetic nephropaths	Diabetic controls (uncomplicated)	Normal controls
No. of subjects	25	25	25
Age (years)	43.2±3.5 (24–69)	46.5±4.2 (27–70)	–
Age at onset of diabetes	11.3±8.0 (2–24)	13.2±9.2 (4–33)	–
Duration of diabetes	30.6±2.3 (20–43)	31.4±2.4 (11–49)	–
HbA1c (%)	9.1±1.6 (8.1–11.8)	8.5±1.5 (7.2–11.2)	–
Plasma glucose (mmol/l)	12.7±0.5	11.0±0.4	–
Insulin dosage (units)	43.8±15.7 (25–94)	58.2±11.5 (20–118)	–
eGFR (ml/min/1.73 m ²)	59.4±4.5 ^a	74.5±3.2	–
M/F	11:14	12:13	10:15

Data are means ± SE (ranges) in years. Levels of plasma, HbA1c, and eGFR are expressed as means + SE in millimole per litre, per cent and millilitre per minute per 1.73 m², respectively. Diabetic nephropaths, uncomplicated and normal controls were defined in the [Materials and methods](#) section

SE standard error, HbA1c haemoglobin A1c, eGFR estimated glomerular filtration rate

^a vs. the uncomplicated, $p=0.02$

glucose) supplemented with 10 % calf serum, 2 mmol/l L-glutamine, 100 units/ml penicillin G sodium and 100 mg/ml streptomycin sulphate with phytohemagglutinin-P at 5 µg/ml and separated into four flasks. The first was cultured for 3 days supplemented with 5 mmol/l D-glucose (normal glucose (NG) concentration within the media), and the second was supplemented with 20 mmol/l D-glucose (high glucose, 25 mmol/l D-glucose final concentration) before culture for the same incubation period. The third flask was cultured for 3 days, supplemented with 5 mmol/l D-glucose before culture, and 10 µg/ml LPS was added for another 24 h (NG + LPS). The fourth flask was cultured for 5 days, supplemented with 20 mmol/l D-glucose before culture, and 10 µg/ml LPS was added for another 24 h (HG + LPS). All of the above cultures were repeated with the addition of 10 µmol/ml of the aldose reductase inhibitor (ARI) sorbinil. At the end of the incubation time, cells were harvested, and protein was extracted from the PBMCs. A portion of the PBMCs in some samples were cultured with mannitol for 3 days (a final concentration at 25 mM) as a positive control.

Extraction of whole protein

Cells were collected, and whole protein was extracted from the cells using 100 µl per flask of a lysis buffer (20 mM Tris-HCl; 150 mM NaCl; 1 mM EDTA; 1 % TX100, pH 7.4). The cells were then left for 15 min, and after which time, the cells were centrifuged to allow the pelleting out of the cell membranes.

The concentration of protein was determined using the Coomassie® Plus Protein Assay Kit (Perbio Science Ltd., Chest, UK).

Determination of AKR1B10 protein levels using Western blotting

Briefly, 50 µg of total proteins was loaded onto a 12 % SDS-PAGE, electrophoresed for 8 h at 150 V and transferred to a nitrocellulose membrane (Amersham, USA) overnight. The membrane was blocked with 5 % non-fat milk, 0.05 % Tween 20 in PBS for 1 h at room temperature before immuno-blotting with a primary mouse antibody against human AKR1B10 at 1:1,000 dilution (Abcam, UK) overnight followed by a horse-radish peroxidase-conjugated goat anti-mouse IgG secondary antibody at a 1:5,000 dilution (Sigma, UK). A mouse anti-human β-actin antibody was used as a loading control. A chemiluminescence kit (Pierce, UK) and the Kodak X-Omat film (Amersham, UK) were used to detect antibody binding. X-ray films were scanned using the BioRad phosphor imager and the band density quantified using the Quantity One (BioRad). Levels of AKR1B10 were normalised to the β-actin loading control.

Statistical analysis

Protein data were analysed through SPSS. The *t* test or one-way analysis of variance was used to test expression levels in response to high glucose and also LPS within and also between groups. A *p* value less than 0.05 was considered to be significant.

Results

The clinical characteristics of patients with type 1 diabetes with (DN) or without (UnComp) diabetic nephropathy and normal controls (NC) are shown in Table 1. There were no differences in age, gender, age at onset of diabetes, duration of diabetes, haemoglobin A1c and plasma glucose levels between the two groups. Estimated glomerular filtration rate was significantly lower in patients with nephropathy compared with uncomplicated subjects (59.4±4.5 vs. 74.5±3.2; $p=0.021$). Figure 1 shows examples of AKR1B10 protein levels from the cells of a patient with diabetic nephropathy, patient with no microvascular complications (uncomplicated) and a normal control.

The mean fold change in AKR1B10 protein levels normalised to baseline (NG) in response to the eight different conditions (NG, NG + L, NG + ARI, NG + LPS + ARI, HG, HG + LPS, HG + ARI and HG + LPS + ARI) in the three different subject groups is shown in Fig. 2. The level of β-actin was similar between all the samples of PBMCs exposed to the

Fig. 1 An example of AKR1B10 protein levels from peripheral blood mononuclear cells (PBMCs) of patients with diabetic nephropathy, patients with no microvascular complications (uncomplicated) and normal control after exposure to the eight conditions (NG, NG + L, NG + A, NG + L + A, HG, HG + L, HG + A and HG + L + A). *NG* normal glucose, *HG* high glucose, *L* lipopolysaccharide, *A* aldose reductase inhibitor (sorbitol). The fold differences for the β -actin (loading control) between the eight different

conditions were not significantly different ranging from 1.0 and 1.2 in all subject groups. There were significant increases in AKR1B10 protein levels in the cells from patients with diabetic nephropathy after exposure to HG and L, and this increase was reduced after the addition of the A. There were no significant increases in AKR1B10 protein in response to HG or L or reduction after the addition of A in the cells from patients with no microvascular complications (uncomplicated) or the normal controls

different conditions (NG, HG, LPS and ARI) (fold increase in the samples supplemented with the different stimuli was up to 1.0 compared to that in samples under normal conditions). This demonstrates that equal amounts of protein were loaded and that variations in AKR1B10 expression under different stimuli were not due to loading errors. There was no significant increase in AKR1B10 expression in response to the addition of 20 mmol/l mannitol (data not shown).

There was a significant increase in AKR1B10 protein levels in response to HG in the cells from patients with DN compared to those under NG conditions, $p < 0.0005$, and this increase was also seen after the addition of LPS, $p < 0.01$. The increase in AKR1B10 protein was significantly reduced by the addition of sorbinil, $p < 0.0005$ (Fig. 2).

There were no significant changes in AKR1B10 protein levels in the cells from patients without complications (uncomplicated) or the normal controls after exposure to HG, LPS or the ARI sorbinil.

After exposure of the PBMCs from patients with DN to LPS under NG conditions, there was a significant increase in AKR1B10 protein compared to uncomplicated patients and normal controls [1.62 ± 0.75 (DN) vs. 1.22 ± 0.35 (uncomplicated (UnComp)), $p < 0.0005$; vs. 1.16 ± 0.15 (NC), $p < 0.0005$]. There was also a reduction in the AKR1B10 level in the normal controls compared to patients with DN after exposure to LPS, but the addition of the ARI [0.53 ± 0.32 (NC) vs. 0.75 ± 0.42 (DN), $p = 0.004$] also increased in response to HG [1.86 ± 0.94 (DN) vs. 1.25 ± 0.56 (UnComp), $p < 0.0005$; vs. 1.09 ± 0.90 (NC),

$p < 0.0005$]. There was also a significant increase in response to HG and LPS in the DNs compared to the uncomplicated and normal controls [2.69 ± 0.19 (DN) vs. 1.35 ± 0.33 (UnComp), $p < 0.0005$; vs. 1.27 ± 0.52 (NC), $p < 0.0005$] (Fig. 2).

Discussion

We have shown in previous studies that AKR1B1 has an important role in the development and progression of diabetic nephropathy in patients with T1D (Srivastava et al. 2005; Chung and Chung 2001; Hodgkinson et al. 2001; Demaine 2003). This is, in part, due to its role in the metabolism of glucose under hyperglycaemic conditions through the polyol pathway, which, in turn, can lead to a number of biochemical and metabolic abnormalities including osmotic and oxidative stress that have been associated with microvascular complications (Brownlee 2005; Giacco and Brownlee 2010; Srivastava et al. 2005). A number of human tissues contain both AKR1B1 and its closely related family member AKR1B10 and the similar catalytic similarities between the two (Crosas et al. 2003), and it is possible that this enzyme may also have a role to play in the pathogenesis of diabetic microvascular complications (Huang et al. 2010). We have shown for the first time that AKR1B10 is expressed in peripheral blood mononuclear cells (PBMCs) and that the expression of AKR1B10 is induced by high glucose (HG) and the inducer of inflammatory stress lipopolysaccharide (LPS). This

Fig. 2 Comparison of AKR1B10 protein expression in patients with diabetic nephropathy, patients with no microvascular complications (uncomplicated) and normal controls. Data are means of fold change from the baseline (NG - L - A) of AKR1B10 protein in the PBMCs from patients with diabetic nephropathy, patients with no microvascular complications (uncomplicated) and normal controls. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.0005$. This graph shows comparisons between the different

subject groups in relation to the different treatments. NG + L - A (DN) vs. NG + L - A (UnComp), $p < 0.0005$; vs. (NG), $p < 0.0005$; NG + L + A (DN) vs. NG + L + A (NG), $p < 0.01$; HG - L - A (DN) vs. HG - L - A (UnComp), $p < 0.0005$; vs. (NG), $p < 0.0005$; HG + L - A (DN) vs. HG + L - A (UnComp), $p < 0.0005$; vs. (NG), $p < 0.0005$. NG normal glucose, HG high glucose, L lipopolysaccharide, A aldose reductase inhibitor

significant increase in AKR1B10 was seen in the PBMCs from patients with DN, and a further increase, after exposure to a combination of both HG and LPS when compared to the other treatment conditions in the DN group. In contrast, there was less of a response to HG and LPS and a combination of both in the PBMCs from patients who had remained free of microvascular complications after 20 years of duration of diabetes as well as the healthy controls. This difference in response was significant between the DNs and the uncomplicated and normal controls. This is very similar to previous studies with AKR1B1 and also cytoplasmic antioxidant enzymes, where there is a distinct difference in response in the cells from patients with DN and those without to HG (Hodgkinson et al. 2001, 2003; Ceriello et al. 2000). It is possible that this difference may have a genetic influence (Hodgkinson et al. 2003; Ceriello et al. 2000), and there is

evidence to support this in relation to AKR1B1 expression levels. We and others have shown that a polymorphism in the promoter region of AKR1B1 is associated with DN and increased expression levels (Heesom et al. 1997; Moczulski et al. 2000; Kao et al. 1999; Zou et al. 2000). The differences we are seeing in the expression of AKR1B10 may also have a genetic influence as a complex microsatellite has been identified in the promoter region of AKR1B10. It has been suggested that this is a potential biomarker for disease (Liu et al. 2009a, b). It is important to investigate this polymorphism in relation to susceptibility to DN and, interestingly, to see if it has a functional effect on the expression of AKR1B10, which may explain the difference we are seeing. The exact biological role of AKR1B10 is still to be fully elucidated; however, there is evidence that it has a role in retinoic acid (RA) metabolism by reducing the level of its production. A reduction in RA may

lead to an increase in inflammatory stress, as it is known to be a suppressor of two inflammatory transcription factors: NF- κ B and AP-1. Evidence has shown that NF- κ B is increased in response to HG and oxidative stress (Rahman et al. 2002), and an increase in its activity has been associated with DN (Yang et al. 2008; Yerneni et al. 1999; Guijarro and Egido 2001; Barnes and Karin 1997); it has also been shown to be induced by LPS (Ramana et al. 2007, 2006; Ramana and Srivastava 2006). AP-1 is known to be activated by oxidative stress (Rahman et al. 2002) and also by the inflammatory cytokine TNF- α (Rahman et al. 2002), which, in turn, is up-regulated by NF- κ B (Navarro-Gonzalez and Mora-Fernandez 2008; King 2008). It is, therefore, possible that in patients with DN, an increase in AKR1B10 expression can lead to cellular damage due to a combination of increased inflammatory stress and, also, oxidative stress through HG and an abnormal response in their antioxidant enzymes. This is further supported by the increasing evidence that inflammation has an important role in the development and progression of DN; however, the exact mechanisms involved are still to be fully understood (Navarro-Gonzalez and Mora-Fernandez 2008; King 2008; Devaraj et al. 2007; Hasegawa et al. 1991).

Although we and others have demonstrated that AKR1B1 expression levels and activity have an important role in the development and progression of DN, it is possible that AKR1B10 also has an important role to play. Previous studies may have lacked the sufficient specificity to distinguish between these two closely related enzymes, and it will be interesting to see in further investigations what role each enzyme has and if there is any interaction between the two in relation to DN.

The addition of the aldose reductase inhibitor, sorbinil, reduced the levels of AKR1B10 protein significantly in the PBMCs from the DNs; we also saw a reduction in the cells from the uncomplicated and normal controls, but this was not as significant. It appears that sorbinil can also effectively reduce AKR1B10 expression as well as AKR1B1 which has been shown in previous studies (Crosas et al. 2003; Liu et al. 2009a, b). Therefore, it is possible that ARIs could be used to reduce the potential damaging effects that may be caused by an increase in AKR1B10 under various cellular stresses (Liu et al. 2009a, b; Takemura et al. 2011), including an increase in inflammation due to the reduction in RA and the resulting increase in NF- κ B and AP-1. Attenuation in the up-regulation of AKR1B10 due to high glucose could also result in a decrease in the cellular proliferation and differentiation, seen in the early stages of DN through reducing the proliferation and hypertrophy of mesangial cells and the excessive formation of extracellular matrix formation. However, the ARI used is not specific to AKR1B10 and will also reduce AKR1B1, and a greater understanding of the exact function of AKR1B10 in the development of DN will require the use of specific AKR1B10.

In this study, we used an antibody that was specific to AKR1B10 to ensure that we were detecting changes in

AKR1B10 expression levels and not AKR1B1. Further investigation of the effects of the increase in AKR1B10 expression due to HG and LPS will need to be carried out carefully to ensure that any effects are due to AKR1B10 and not AKR1B1 due to the close relation between the two enzymes. The use of specific siRNA to each of the enzymes to inhibit their expression would allow changes within the cells to be associated with a particular enzyme.

In conclusion, this is the first study to show the expression of AKR1B10 in peripheral blood mononuclear cells and the induction of this enzyme in response to high glucose and lipopolysaccharide. We found striking differences in the expression profile of AKR1B10 to HG and LPS in patients with nephropathy compared to those without and normal controls which suggests that AKR1B10 may have a role in the pathogenesis of DN. This role may be part of the inflammatory mechanisms that have been recently linked to the development and progression of DN.

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