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Research paper

Polymorphic differences in the SOD-2 gene may affect the pathogenesis of nephropathy in patients with diabetes and diabetic complications

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ABSTRACT

The effective treatment of diabetes and the prevention of diabetic complications may be improved by a better understanding of the antioxidant function of intracellular defences against oxidative stress. Polymorphisms in antioxidant genes may determine cellular oxidative stress levels as a primary pathogenic role in diabetes and/or in its complications. SOD-2 was investigated in patients with type 1 diabetes mellitus (T1DM) to ascertain if specific genotypes have any protective influences in the pathogenic mechanisms in diabetes and/or in several different complications, including retinopathy, nephropathy and diabetic controls compared to normal healthy controls.

Method: 278 (136M:142F) T1DM patients and 135 (72M:63F) normal, healthy controls were investigated for SOD-2 polymorphism in the mitochondrial targeting sequence with Ala/Val (C-9T) substitution.

Results: A significant difference in the C-9-T genotype was observed between patients and normal controls but not between diabetic controls and patients with complications. There were significantly more of the diabetic control (DC, $n = 62$) group (11.3%) than the patients with diabetic nephropathy (DN, $n = 73$) (1.4%) with the CC genotype ($p = 0.03$ and $\chi^2 = 4.27$, OR = 9.16 ($1.08 < OR < 204.03$)). Further significance was found between normal healthy controls (11.4%) and patients with nephropathy (1.4%) with the genotype CC ($p = 0.03$, $\chi^2 = 4.68$, OR = 0.11 ($0.00 < OR < 0.87$)).

No significant differences were found between these groups for the allelic frequency or between the different complication groups after correction for the number of groups.

All groups were in Hardy Weinberg equilibrium.

Conclusion: The SNP in SOD-2 results in a substitution of C to T, which causes an amino acid change from alanine to valine. The variation in the SOD-2 leader signal affects the processing efficiency of the enzyme. A significantly greater proportion of the diabetic control group had the CC genotype suggesting antioxidant protection against diabetic nephropathy. The healthy control group also had a higher incidence of the protective genotype, which may suggest protective influences from the antioxidant gene in the CC form.

1. Introduction

Effective treatment of diabetes and the prevention of microvascular complications in both type 1 and type 2 diabetes may be improved by a better understanding of the antioxidant function of intracellular defences against oxidative stress (OS) (Baynes, 1991; Michels, 1994; Naudi et al., 2012). The generation of dangerous reactive intermediates, known as reactive oxygen species (ROS), is a by-product of normal aerobic metabolism and plays an important role in the pathogenesis of the long-term complications of diabetes. All the hyperglycaemia-induced pathways produce ROS that in turn act as intercellular signals to continue the pathway cycles (Brownlee, 2001; Brownlee, 2005; Salahudeen et al., 1997). Hyperglycaemia induced metabolic imbalances, involve ROS and cause OS (Cohen et al., 2012). Further, increase in the cytosolic ratio of free NADH/NAD+ results in pseudohypoxia, which play important roles in mediating early neural and vascular dysfunction. There are similar mechanisms involved in true hypoxia (Guigliano et al., 1996).

It has been reported that there is an early molecular event involving an increase in mitochondrial mass and mtDNA content in response to exogenous and endogenous oxidative stress (Lee et al., 2000). ROS from mitochondria induce cyclo-oxydase gene expression and suggests a potential role of ROS in diabetic nephropathy (Kiritoshi et al., 2003).

Abbreviations: T1DM, type one diabetes mellitus; T2DM, type two diabetes mellitus; IDDM, insulin dependent diabetes mellitus; DMI, diabetic myocardial infarction; DC, diabetic control; DN, diabetic nephropathy; DR, diabetic retinopathy; SD, diabetic patients with short duration of disease; ROS, reactive oxygen species; OS, oxidative stress; F, female; M, male; CAT, catalase; MNSOD, SOD-2, type two superoxide dismutase; ALR2, aldose reductase gene; UV, ultra violet; WHO, World Health Organization; H_2O_2, hydrogen peroxide.

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Enzymic systems are part of a cell's line of defence against the lethal or mutagenic damage caused by OS by removing ROS from the cell and involve enzymes such as catalytic superoxide dismutases (SOD): copper/zinc-dependent SOD (CuZnSOD) in the cytosol, manganese-dependent SOD (MnSOD) in the mitochondria and catalase (CAT) in the cytosol and peroxisomes (Michiels et al., 1994).

SOD catalyses the dismutation of hydrogen peroxide and superoxide into oxygen, enabling cell repair and reducing the damage inflicted by OS. Hydrogen peroxide is further broken down to water by catalase or peroxidase. ROS induces this antioxidant enzyme expression in tissues but defective production or action could result in OS and ROS tissue damage ultimately leading to cell death (Beckman and Ames, 1998).

Decreased levels of SOD-2 may contribute to the development of certain diseases. Mice without the gene that encodes SOD-2 die 10 days after birth with cardiomyopathy and lipid accumulation in the liver and skeletal muscles (Li et al., 1995a). In animal cells decreased SOD-2 and catalase levels were observed in breast cancer, adenomas and leukaemia (Sun et al., 1993). A polymorphism in SOD-2 (Ala16Val) was shown to modulate the import of human SOD-2 into rat liver mitochondria (Sutton et al., 2003).

Differences in antioxidant expression may explain a predisposition of a patient with diabetes to diabetic complications such as nephropathy, neuropathy, cardiovascular disease or retinopathy. ROS are increasingly formed in diabetes mellitus by the auto-oxidation of glucose and glycosylated proteins. Hyperglycaemia leads to the activation of the polyol pathway and contributes to the formation of triose phosphate and its auto-oxidation which results in α-oxaldehyde and H_2O_2 (Negre-Salvayre et al., 2009). Defective antioxidant expression may be partly due to polymorphic differences in the genes encoding the antioxidant enzymes. SOD-2 expression was decreased in patients with T1DM and patients with T2DM and was determined by the SOD-2 genotype (Flekac et al., 2008). There is growing evidence to suggest that polymorphisms in the promoter region of the aldose reductase gene (ALR2) are associated with susceptibility to nephropathy, retinopathy and neuropathy and differing levels of the gene's expression (Demaine et al., 2000; Heesom et al., 1998) Antioxidant responses to hyperglycaemia have shown that SOD-2 responses did not change between diabetic patient complication groups or in normal controls (Hodgkinson et al., 2003). Although SOD-2 is involved in controlling dioxygen toxicity in an organelle of extreme oxidative load, the mitochondria, decreased levels of SOD-2 may contribute to the development of certain diseases. Normalising mitochondrial superoxide production blocks three pathways of hyperglycaemic damage (Nishikawa et al., 2000). Antioxidant therapy has proved promising in preventing the onset of diabetic heart disease (Wold et al., 2005).

Various animal studies have shown the effects of deficient antioxidant function and mice without the gene that encodes SOD-2 die 10 days after birth with cardiomyopathy and lipid accumulation in the liver and skeletal muscles (Sentman et al., 2006). In other animal cells, decreased SOD-2 and catalase levels were observed in breast cancer, adenomas and leukaemia (Shimizu et al., 2010; Salvemini et al., 1999). In mouse models with heart muscle tissue specific MN-SOD conditional knockout mice that were developed to analyse the pathological role of superoxide injuries in adult tissues, they developed progressive dilated cardiomyopathy with molecular defects in mitochondrial respiration (Kobayashi et al., 2004).

Treatment of diabetic animals with SOD/catalase mimetics prevents the diabetes induced oxidative inactivation of eNOS and aortic prostacyclin synthase (both antiartherogenic enzymes), which are usually induced during ROS overproduction during hyperglycaemia (Tiwari et al., 2009; Vojtková et al., 2013).

The SOD-2 targeting signal sequence polymorphism has been identified on chromosome 6q 25 and may be in linkage with the susceptibility genes IDDM5 (6q22) and IDDM8 (6q27), discovered by Todd when screening the human genome for T1DM related genes (Todd and Farrall, 1996). A polymorphism in the mitochondrial targeting signal sequence could affect the transport of the enzyme through the mitochondrial membrane and a defect may alter the membrane receptor recognition site resulting in less of the enzyme protein entering the cell thus lowering the antioxidant response to oxidative stress.

Ala/Ala homozygotes for a polymorphism in the SOD-2 mitochondrial targeting sequence (Ala -9 Val substitution) has been found to be significantly lower for patients with diabetic nephropathy (DN) than patients without nephropathy whereas the Val/Val genotype was significantly higher in the DN group in a Russian cohort (Chistyakov et al., 1999). Different results have been observed in different populations and ethnic differences have been observed with this polymorphism (Van Landeghem et al., 1999). A recent study shows that impaired oxidative balance may have a prognostic significance on disease activity and determines the severity or the disease outcome in chronic HCV patients (Houldsworth et al., 2014).

Manganese superoxide dismutase (SOD-2) is found in the mitochondria in nearly all cells and with a molecular mass of 40,000 kDa it consists of four subunits each of which probably contains a manganese atom. The localisation of SOD-2 to chromosome 6 (6q25) (Todd and Farrall, 1996) and some of the features of the SOD-2 gene are typical of housekeeping genes (Church et al., 1992; Dynan et al., 1986).

Mutations in the SOD-2 gene have also been associated with idiopathic cardiomyopathy (IDC), sporadic motor neuron disease, and cancer (Muller et al., 2007; Li et al., 1995b; Van Remmen et al., 2003). The role of mitochondrial oxidative stress by ROS is associated with the pathogenesis of target organ damage in hypertension and the role of mitochondrial antioxidants such as SOD-2 shows promising strategies to reduce the development of endothelial dysfunction, cardiac hypertrophy, and renal and cerebral damage in hypertension (Rubattu et al., 2014).

2. Materials and methods

2.1. Patients included

Type 1 diabetic cases were included for the SOD-2 polymorphism analysis. Cases were subdivided into groups according to the presence or absence of microvascular complications in long-term diabetes.

Patients were recruited from the Diabetic Centre at Derriford Hospital, Derriford, Plymouth and from Kings College Hospital.

Patients with T1DM diagnosed using the WHO criteria for 10 years or more. Diabetic controls must have been diagnosed for 20 years without further complications such as nephropathy, neuropathy, retinopathy or cardiovascular disease. There were 278 patients with T1DM available for the study (see Table 1)

2.2. Patient with diabetes and complications

Nephropathy (DN) was described in patients with more than 10 years of diabetes and proteinuria at least 3× in 12 months. Retinopathy (DR) was defined in patients with more than 5 dots or blots per eye, hard or soft exudates, new vessel evidence of maculopathy or vitreous haemorrhage. Short duration (SD) patients had been diagnosed with diabetes for less than 10 years whereas uncomplicated (DC) patients displayed no complications after a 20 year duration of T1DM.

2.3. Controls

135 ethnically matched controls were studied. Control DNA was obtained from the cord blood of European Caucasoid subjects collected sequentially after normal obstetric delivery from the Obstetric Department, Derriford Hospital (Plymouth, UK).

Ethics committee approval and patient consent were obtained for all studies performed.

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2.4. Genetic studies

Genomic DNA was extracted conventionally from whole blood using a 'salting out' method. The restriction site was found at −9 on the mitochondrial targeting sequence of the manganese superoxide dismutase, which is a C to T substitution resulting in an amino acid change of alanine to valine.

Two primers were used to amplify SOD-2 (ala, −9, val), the forward primer was 5′-AGC CCA GCC TGC GTA GAC-3′ and the reverse primer 5′-TAC TTC TCC TCG GTG ACG-3′ (Fig. 1).

The restriction enzyme used to digest the amplified fragment was BsaW1 (*Bacillus stearothermophilus* W1718 Chen) (5′A^CCGG A3′, 3′T GGCC^T 5′). The C1183T polymorphism in the mitochondrial sequence of MnSOD was digested by BsaW1 in a water bath at 60 °C for 90 min produced two fragments of 82 and 164 bp. Samples where the cut site was abolished due to the presence of the 'T' allele produced fragments of 246 bp. The migration of the DNA was visualised under ultra violet light and the bands were photographed using a transilluminator linked to specialist computer software. In order to genotype the samples, the position of the bands was determined relative to the DNA ladder fragments.

2.5. Statistical analysis

The frequency of the alleles and genotypes in both patient subgroups and controls were compared for significance, using contingency tables and chi-squared test with Yates correction where appropriate (Table 2). P values of <0.05 were considered to be significant. We also included odds ratios with 95% confidence limits where appropriate.

2.6. Hardy–Weinberg distribution

In a non-selected population, the relative frequencies of different alleles tend to be constant and are described by a single equation. Several factors may distort the gene frequencies in a population. The patients infected with diabetes were recruited from the South West of England as were the healthy control subjects. A high frequency may indicate the possibility that evolutionary forces are in operation and applying selective pressure in favour of heterozygotes or homozygotes for mutant genes that cause the more common inherited disorders. We tested for Hardy Weinberg distribution in the population of the genotypes that were studied using the calculation ($p^2 + 2pq + q^2 = 1$). The frequency of C = p and the frequency of T = q. This tested for genetic variation of a population in equilibrium (Emigh, 1980).

3. Results

3.1. SOD-2 genotype for patients with T1DM

We determined the genotype frequency of 278 patients with T1DM for a C/T substitution polymorphism on the mitochondrial targeting sequence of the manganese superoxide dismutase gene.

Patients with T1DM diagnosed using the WHO criteria for 10 years or more. Diabetic controls must have been diagnosed for 20 years without further complications such as nephropathy, neuropathy, retinopathy or cardiovascular disease. Non-diabetic controls were without any of the above complications. The patients with T1DM (n = 278, 136M:142F) available for the study had a mean age of 45.6 years ± 1.08 SEM with a mean duration of diabetes of 30.9 years ± 1.01 SEM. The normal controls (n = 135, 72M:63F) were obtained from the cord blood of European Caucasoid subjects collected sequentially after normal obstetric delivery from the Obstetric Department, Derriford Hospital (Plymouth, UK). The subjects had no family history of T1DM and were not infected with HCV. All differences were corrected using the Yates correction.

Patient complications were nephropathy (DN) which was defined as >10 years of diabetes and proteinuria at least three times in 12 months (n = 73, 31M:42F) an average age of 47.8 ± 1.96 SEM and a mean duration of disease of 33.0 years ± 1.64 SEM. Diabetic retinopathy (DR) was defined as >5 dots or blots per eye, hard or soft exudates, new vessels evidence of maculopathy or vitreous haemorrhage and the group had a mean age of 62.8 years ± 2.49 SEM (n = 15, 7M:8F). The uncomplicated diabetic controls (DC) had no diabetic complications after 20 years of duration of T1DM and an average age of 52.0 ± 2.02 SEM (n = 62, 27M:35F). There was also a group of patients that had only been diagnosed for a short period of time (SD) with a mean age of 30.0 years ± 2.16 SEM (n = 33, 18M:15F) (see Table 1).

There were significantly more of the diabetic control (DC) group (11.3%) than the patients with diabetic nephropathy (DN) (1.4%) with the CC genotype (p = 0.03 and $\chi^2 = 4.27$, OR = 9.16 (1.08 < OR < 204.03)). Further significance was found between normal healthy controls (17.0%) and patients with nephropathy (1.4%) with the genotype CC (p = 0.03, $\chi^2 = 4.68$, OR = 0.11 (0.00 < OR < 0.87)).

4. Discussion

The role of free radical reactions in protein oxidation, DNA damage and lipid peroxidation is strongly debated in relation to human disease and has been implicated in many disease states. It is not clear whether ROS are solely a major cause of tissue damage in disease or if they need to be accompanied by other factors as well as the tissue injury. It is clear that free radical reactions occur more readily than normal in diseased or damaged tissues and this may exacerbate disease. Increased oxidisability of damaged tissues can be due to the inactivation or leakage of antioxidants from cells.

Proliferative cells that are exposed to sub-cytotoxic OS such as H_2O_2, UV, ethanol, etc. display mitochondrial DNA deletions, cell morphology, histochemistry changes, cell cycle regulation and gene expression differences (Sozou and Kirkwood, 2001). Polymorphic genetic differences may change the antioxidant gene expression in a way similar to these somatic mutations caused by OS.

The single nucleotide polymorphism results in a substitution of C to T, which causes an amino acid change from alanine to valine. The variation

Table 1
Clinical characteristics of the T1DM patients and healthy controls including the number in the study, the present age of the cases and the age of diagnosis as well as the number of years since the diagnosis of T1DM.

Patient demographics and clinical characterisation of T1DM subgroups					
Diagnosis	All T1DM cases[a]	DC	DN	DR	SD
Number of subjects (n)	278	62	73	15	33
Age/years ± SEM	45.6 ± 1.08	52.0 ± 2.02	47.8 ± 1.96	62.8 ± 2.49	30.0 ± 2.16
Age of onset/years ± SEM	17.0 ± 0.78	16.0 ± 1.24	16.0 ± 1.58	28.0 ± 2.51	21.0 ± 2.26
Duration of diabetes/years ± SEM	30.86 ± 1.01	35.1 ± 1.35	33.0 ± 1.64	36.1 ± 2.75	10.1 ± 0.43
Sex M:F	136:142	27:35	31:42	7:8	18:15

Normal controls n = 113 (M:F = 60:53).
The complication groups are defined as DC = diabetic control (no complications for >20 years), DN = patients with nephropathy, DR = patients with retinopathy and SD are patients that have had T1DM for a short duration.
[a] 95 cases were not characterised by a complication.

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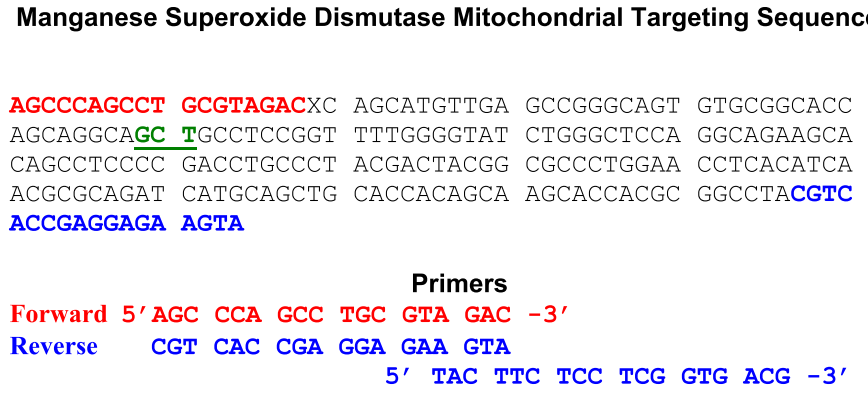

Fig. 1. Manganese superoxide dismutase mitochondrial targeting sequence.

in amino acid from alanine to valine in the SOD-2 leader signal affects the processing efficiency of the enzyme. The amino acid change is thought to give a conformational change from an alpha helix to a beta sheet and this may result in mistargeting due to poor receptor recognition. The valine form may be less efficiently transported into the mitochondria than the alanine form of the enzyme. Studies have indicated that basal SOD-2 activity may be highest for Ala/Ala, followed by Ala/Val and then Val/Val (Chistyakov et al., 2001; Shimoda-Matsubayashi et al., 1996). It is postulated that the functional polymorphism V16A affects the localisation of MnSOD into the mitochondrial matrix and therefore its ability to scavenge superoxide radicals (Sutton et al., 2003).

Recent studies of patients with T1DM have shown that homozygosity for the MnSOD Val allele is associated with an increased risk of diabetic nephropathy (Chistyakov et al., 2001). An association study using this polymorphism also showed significant allelic deviation in Parkinson's disease (Shimoda-Matsubayashi et al., 1996). Another cohort of patients with T1DM was found to have a positive association of the Val/Val genotype with retinopathy and nephropathy (Möllsten et al., 2007; Hovnik et al., 2009). The polymorphism was also associated with T2DM development and in patients with Type 2 diabetic nephropathy (Yang et al., 2007; Liu et al., 2009; Nakanishi et al., 2008). A meta-analysis of the V16A polymorphism of SOD-2 of several studies associated the gene with diabetic nephropathy and cardiovascular disease in patients with T1DM (Möllsten et al., 2011).

The results reported in this paper agree with other evidence, where there was a lower frequency of 'CC' homozygotes in the DN and other patients with complications than those without complication but differed with on the frequency of 'TT' homozygotes as they found no significant differences in the allelic comparisons. Similar levels of heterozygosity were found in our control group as Chistyakov's controls and we agree that there is an increase in Ala/-9/Val dimorphism in DN patients. A trend in a higher frequency of heterozygosity was reported here whereas Chistyakov reported a significant difference (Chistyakov et al., 1999).

The role of free radical reactions in protein oxidation, DNA damage and lipid peroxidation is strongly debated in relation to human disease and has been implicated in many disease states. It is not clear whether ROS are solely a major cause of tissue damage in disease or if they need to be accompanied by other factors as well as the tissue injury. It is clear that free radical reactions occur more readily than normal in diseased or damaged tissues and this may exacerbate disease. Increased oxidisability of damaged tissues can be due to the inactivation or leakage of antioxidants from cells.

Previous to this study we investigated a cohort of patients with diabetes and their antioxidant responses to hyperglycaemia has shown that SOD-2 responses did not change between patient with diabetic complication groups or in normal controls (Hodgkinson et al., 2003). Different results have also been observed in different populations and ethnic differences have been observed with this polymorphism (Van Landeghem et al., 1999).

The SNP in SOD-2 results showed significant difference in a substitution from C to T, between patient groups. A significantly greater proportion of the diabetic control group had the CC genotype suggesting antioxidant protection against diabetic nephropathy. The healthy control group also had a higher incidence of the protective genotype, which may suggest protective influences from the antioxidant gene in the CC form.

The findings from this study support the hypothesis that functional impairment of the MnSOD gene is associated with an increased risk of diabetic nephropathy and that the V allele of the SOD2 rs4880 polymorphism increases the risk of diabetic nephropathy in patients with T1DM.

Table 2
The % frequency of the SOD-2 genotypes and alleles for a population of patients with diabetes and without diabetic complications.

Percentage genotype frequency of SOD-2 mitochondrial targeting polymorphism in T1DM patients					
Genotype frequency	Diabetic patients	Diabetic controls	Diabetic with nephropathy	Diabetic with retinopathy	Normal controls
Number of cases (n)	n = 278 136M:142F	N = 62 27M:35F	n = 73 31M:42F	n = 15 7M:8F	n = 135 72M:63F
C/C	10.1% (28)	11.3% (7)[1]	1.4% (1)[a]	6.7% (1)	17.0% (23)[b]
C/T	65.1% (181)	64.5% (40)	76.7% (56)	60.0% (9)	60.0% (81)
T/T	24.8% (69)	24.2% (15)	21.9% (16)	33.3% (5)	23.0%(31)
Allelic frequency					
Number of alleles or chromosomes	n = 556	n = 124	n = 146	n = 30	n = 270
C	41.6%(237)	43.5% (54)	39.7% (58)	36.7% (11)	47.5% (128)
T	57.4%(319)	56.5% (70)	60.3% (88)	63.3% (19)	52.5% (142)

All patients and control groups were in Hardy Weinberg equilibrium.
No other significant differences were found.
[a] Significant difference between diabetic controls (11.3%) and patients with diabetic nephropathy (1.4%), $p = 0.04$, $\kappa^2 = 4.27$ for CC, OR = 9.16 (1.08 < or < 204.03).
[b] Significant difference between normal controls (11.4%) and patients with diabetic nephropathy (1.4%), $p = 0.03$, $\kappa^2 = 4.68$ for CC, OR = 0.11 (0.00 < OR < 0.87).

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Other findings support the protective effect of Ala at rs4800 against the damaging effects of oxidative stress and suggest that distant linkage equilibrium may exist with another true disease causing gene variant (McKnight et al., 2012) A recent meta-analysis suggested that C allele of C47T polymorphism in SOD2 gene has protective effects on risk of DMI, diabetic nephropathy and diabetic retinopathy (Möllsten et al., 2011). A full understanding of the mechanisms is still unclear and further research is required to clarify this and to consider if SOD-2 therapy may be advantageous to patients with diabetes (Salvemini et al., 1999).

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