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11

Diabetic Nephropathy: Current and Novel Therapeutic Approaches to Prevent Its Development and Progression

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1. Introduction

Diabetes is a metabolic disorder characterised by chronic hyperglycaemia, hypertension, dyslipidaemia, microalbuminuria and inflammation. Moreover, there are a number of vascular complications associated with this condition including retinopathy, neuropathy and nephropathy. Diabetic nephropathy is the major cause of end-stage renal disease in Western societies affecting a substantial proportion (25-40%) of patients with diabetes. Diabetic nephropathy is defined as a progressive decline in glomerular filtration rate, accompanied by proteinuria and other end-organ complications such as retinopathy.

It is widely accepted, that diabetic nephropathy is the product of hemodynamic and metabolic factors which act in concert and drive its development and progression. Metabolic factors include hyperglycaemia, hyperlipidaemia and advanced glycation. Hemodynamic factors include alterations in flow and pressure and the activation of the Renin-Angiotensin system (RAS). Together, the hemodynamic and metabolic factors activate common downstream signalling pathways, which potentiate the activation of target growth factors and signalling pathways which likely drive the development of DN. At present the most effective therapeutics for the treatment of DN target the renin-angiotensin system. Unfortunately, whilst they slow down the progression of DN they do not prevent it and thus novel therapeutics and potential targets required.

In recent times the downstream intracellular signalling pathways and their modulators have been central focus for the investigation of novel therapeutic targets for the treatment of DN. These targets include advanced glycation end products (AGEs) and their receptors, glucose transport molecules, NFκB, ROS, PKC, inflammatory molecules, including adipokines, chemokines, adhesion molecules and pro-inflammatory cytokines. Moreover, pro-fibrotic molecules , including EGF, VEGF, CTGF and arguably the most important, TGF-β, which are known to potentiate the morphological alterations associated with DN have also been targeted. Recently, epigenetic alterations, including histone, DNA methylation, metabolic memory and microRNA's have demonstrated their potential as novel therapeutic targets in

the area of DN. Importantly a number of these potential therapies are the focus of clinical trials or are in pre-clinical investigations.

In summary this chapter will investigate the hemodynamic, metabolic and epigenetic factors which drive the development of diabetic nephropathy and their subsequent downstream signalling pathways. Importantly, we will discuss the limitations of current therapeutic strategies and development of novel therapeutic targets which are presently in either pre-clinical experimental investigations or clinical trials.

2. Diabetes

Today, it is estimated that approximately 180 million individuals worldwide have diabetes and WHO predicts that this is likely to double by the year 2030. The incidence of diabetes is increasing across the board, irrespective of age, sex or ethnicity (Sowers and Stump 2004). Diabetes is a metabolic disorder characterised by chronic hyperglycaemia, and often co-morbidities such as hypertension, dyslipidaemia and inflammation, with the major types being type 1 (insulin-dependant) or type 2 (commonly non-insulin dependant) (Sowers and Stump 2004; O'Connor and Schelling 2005). Both forms of diabetes are associated with micro- and macrovascular complications which include retinopathy, neuropathy, cardio/cerebrovascular disease and nephropathy which are the major cause of mortality and morbidity in diabetic patients (Cooper, Gilbert et al. 1998; Giacchetti, Sechi et al. 2005).

3. Diabetic nephropathy

Diabetic nephropathy is defined as a progressive decline in glomerular filtration rate, accompanied by proteinuria and other end-organ complications such as retinopathy (O'Connor and Schelling 2005). Diabetic nephropathy progresses to end-stage renal disease via a number of stages including normoalbuminuria, microalbuminuria/incipient diabetic nephropathy, macroalbuminuria and finally end-stage renal disease (Giacchetti, Sechi et al. 2005; O'Connor and Schelling 2005). Progression to end stage renal disease is enhanced by hyperglycaemia, hypertension and proteinuria, which are all common in diabetes (Cooper 1998; Mene, Festuccia et al. 2001; Marshall 2004; Wolf 2004).

Renal disease in diabetic patients is characterised by hemodynamic (hyperfiltration and hyperperfusion) as well as structural abnormalities (glomerulosclerosis, alterations in tubulointerstitium including interstitial fibrosis) and metabolic changes (Cooper 2001). More importantly, it appears that all renal cell types are affected by hyperglycaemic injury including glomerular podocytes, mesangial and endothelial cells, tubular epithelial cells, interstial fibroblasts, and vascular endothelia (Kanwar, Wada et al. 2008). Within glomeruli, there is thickening of basement membranes, mesangial expansion and hypertrophy and glomerular epithelial cell (podocyte) loss (Bohlender, Franke et al. 2005). In conjunction, disease progression is also seen in the tubulointerstitial compartment causing expansion of tubular basement membranes, tubular atrophy, interstitial fibrosis and arteriosclerosis (Marshall 2004).

To date, the most effective clinical treatments to prevent the progression of diabetic nephropathy are strict blood glucose control and anti-hypertensives (1998; 2002; 2003). Unfortunately, present therapies have failed to prevent new cases of diabetic nephropathy and progression as such novel therapeutic approaches are required. It is widely accepted that there metabolic, hemodynamic and genetic components of diabetic nephropathy. Novel

therapeutics which are either in pre-clinical or clinical investigations target these factors in the hope of achieving the ultimate goal, prevention of diabetic nephropathy.

4. Potential therpeutic targets and approaches

4.1 Modulating hemodynamic pathways

Hyperfiltration, which presents as a marked increase in glomerular filtration rate, is widely recognised as being an early marker of diabetic nephropathy (Kanwar, Sun et al.; Anderson and Brenner 1988). Elevations in intra-renal pressure or glomerular capillary pressure are thought to induce the development of hyperfiltration thus highlighting the importance of the hemodynamic pathways in DN. Furthermore, the UK prospective diabetes study in type 2 diabetic patients, highlights the importance of hemodynamic influences in the development of DN. Diabetic subjects randomised to receive tighter blood pressure control, exhibited a concomitant reduction in microalbuminuria and clinical proteinuria (1998) To date the most effective treatments for both type 1 and type 2 diabetic patients to retard the progression of diabetic complications, are anti-hypertensives which target the renin-angiotensin system (Lewis, Hunsicker et al. 1993; Brenner, Cooper et al. 2001).

4.2 The Renin-Angiotensin System (RAS)

The renin-angiotensin system (RAS) is a co-ordinated hormonal cascade, which modulates vasoconstriction and facilitates renal-sodium absorption to maintain blood pressure control. The RAS cascade is initiated by the production of renin, which is released from renal juxtaglomerular cells, and converts angiotensinogen to angiotensin I. Angiotensin I, an inactive hormone, is subsequently cleaved into Angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II drives the RAS and elicits its effects by binding to cellular receptors, the Angiotensin II type I receptor (AT1) or angiotensin type 2 receptor type II (AT2). It was originally postulated that AT1 was the primary receptor and modulator of the actions of Ang II, however in recent years it has been widely accepted that AT1 and AT2 elicit opposing actions upon ligand interaction with Ang II. The RAS is known to exist both systemically and locally in a number of different organs throughout the body including kidney, and vasculature (Wiecek, Chudek et al. 2003; Wolf 2004). Activation of the local renal RAS appears to be independent of the systemic RAS. In diabetes, the local RAS has been found to be up-regulated, in particular within the kidney, whilst the systemic RAS appears to be down-regulated (Gilbert, Krum et al. 2003; Wiecek, Chudek et al. 2003; Schrijvers, De Vriese et al. 2004; Forbes, Fukami et al. 2007).

To date the most effective treatments for diabetic nephropathy target the RAS. Whilst they slow down the progression of nephropathy, Clinical studies such as the RENAAL have demonstrated that these compounds do not prevent the relentless progression to end stage renal disease.

4.3 The endothelin pathway

The endothelin pathway has also been shown to be involved in the development and progression of diabetic nephropathy. There are three recognised endothelin proteins: ET-1, ET-2 and ET-3, all of which share a high level of homology and have demonstrated localisation in a variety of cell types. These vasoactive proteins bind to their receptors ET_A, ET_B, and ET_C. ET_A receptors have been shown to induce vasoconstriction and mitogenesis whilst ET_B receptors has been shown to induce vasoconstriction and vasodilatation (Seo,

Oemar et al. 1994; Roux, Breu et al. 1999; Candido and Allen 2002). Importantly, within the diabetic kidney, ET-1 has been found to be elevated and altered expression of the receptors has also been reported. In addition, modulation of this pathway through the employment of ET antagonists has been shown to reduce renal extracellular matrix (ECM) accumulation diabetic rats (Jandeleit-Dahm, Allen et al. 2000; Fukami, Cooper et al. 2005). Bosentan, an ET_A and ET_B receptor antagonist has demonstrated renoprotective benefits in the diabetic rat which was comparable to enalapril. Currently there are number of clinical trials examining the benefits of ET antagonists such as bosentan in diabetic nephropathy.

5. Modulation of metabolic pathways

5.1 Glycaemic control

A range of metabolic abnormalities in addition to hyperglycaemia, are seen in the diabetic milieu. However, it is obvious from studies in diabetic patients, that an elevation in circulating glucose is the predominant metabolic abnormality and strict glycaemic control, remains the ideal therapeutic approach to halt the progression of complications (1998; 2002). As well as promoting the formation of AGEs, chronic hyperglycaemia is also associated with increased inflammation and expression of associated inflammatory cytokines, such as MCP-1 (monocyte chemoattractant protein-1) (Dragomir, Tircol et al. 2006), and CTGF (connective tissue growth factor) (Makino, Mukoyama et al. 2003), elevated production of ROS (reactive oxygen species) and activation of a number of signalling pathways which are involved in diabetic nephropathy. At present glycaemic control is achieved through a number of approaches including improving insulin sensitivity via agents such as glitazones, increasing pancreatic insulin production with sulfonylureas and meglitinides, reducing hepatic glucose production with the administration of biguanides, limiting post-prandial glucose absorption with α-glucosidase inhibitors (Wagman and Nuss 2001; Fukami, Cooper et al. 2005).

A novel approach to modulate post-prandial glucose absorption is via targeting glucagon-like peptide-1 (GLP-1). GLP-1 is an incretin hormone which is known to stimulate insulin secretion, increase pro-insulin biosynthesis and improve pacreatic beta-cell viability. Recently it has been demonstrated that GLP-1 also posesses a number of extra pancreatic functions including anti-apoptotic and anti-inflammatory effects. The actions of GLP-1 are also modulated via an endogenous circulating enzyme DPP IV (dipeptidyl peptidase inhibitors). At present GLP-1 analogues and inhibitors of DPP-IV are under pre-clinical investigation for diabetic nephropathy. Specifically, administration of GLP-1 in an experimental model of type-1 diabetes exhibited renoprotective benefits independant of glucose control thus warrant further investigation (Kodera, Shikata et al.)

5.2 Modulation of glucose uptake

The initial step of glucose signalling it thought to be the translocation of glucose into the cells. Glucose uptake into renal cells is facilitated by various glucose transporters including SGLT2 (sodium-glucose transporter-2) , GLUT-1(glucose transporter -1) and GLUT-4 (glucose transporter-4). Hyperglycaemia is thought to induce an increase in expression and /or activity of these receptors which results in elevated intracellular glucose, which is one of the fundamental drivers for the development of diabetic nephropathy. One of the pathological outcomes of increased glucose transport is increased aldose reductase expression and up-regulation of PKC-MAPK (Protein kinase C- mitogen activated protein kinase) pathways which lead subsequent elevation in ECM (extracellular matrix) proteins such as collagen IV and fibronectin which are pivotal to the

development of fibrotic lesions associated with DN (Kanwar, Sun et al.). Moreover, TGF-β (Transforming growth factor-β) is known to promote GLUT-1(glucose transporter-1) expression and facilitate elevations in intracellular glucose (Fukami, Yamagishi et al. 2007). Inhibitors of facilitative glucose transporter-2 (SGLT-2) (T-1095), have demonstrated potential as therapeutics for diabetic nephropathy in experimental models of type 1 diabetes. Administration of T-1095, a synthetic inhibitor of SGLT, reduced plasma glucose and urinary AER and a concomitant decrease in gene expression GLUT-2 (Fukami, Yamagishi et al. 2007). Thus targeting glucose transporters has exhibited renoprotective benefits and further investigation is warranted.

5.3 Advanced glycation end-products

AGEs are a heterogeneous and complex group of modifications, which play an important role in the development of diabetic nephropathy. They often present as a yellow-brown pigmentation, may be fluorescent and a number are primarily cross-links between proteins (Brownlee 1992; Brownlee 1995; Kalousova, Zima et al. 2004). AGEs are formed as a result of non-enzymatic biochemical reactions initiated as part of the Maillard Reaction. This reaction is a multi-step process, where a reactive carbonyl from glucose or its derivatives, are attached commonly to lysine and arginine residues on proteins, amino acids and nucleic acids (Njoroge and Monnier 1989; Ziyadeh, Cohen et al. 1997). Following further condensation, rearrangement and other reactions, the intermediate compounds of which some are "Schiff" bases and amadori products, are further irreversibly modified to become advanced glycation end products (AGEs) (Njoroge and Monnier 1989; Schrijvers, De Vriese et al. 2004). Physiologically, advanced glycation is thought to play an important role in the identification of senescent molecules, which are then subsequently cleaved and cleared, primarily via the kidneys (Jakus and Rietbrock 2004).

Within the body, AGEs accumulate from both endogenous and exogenous sources. Intracellularly, AGEs are formed as a by-product of a number of important biochemical reactions including oxidation of glucose to glyoxal, decomposition of amadori products and the fragmentation of glyceraldehydes. The reactive intracellular intermediates formed during these reactions, such as methylglyoxal, react with the amino groups of both intracellular and extracellular proteins to form AGEs (Brownlee 1992; Bierhaus, Hofmann et al. 1998).

AGEs may be broadly categorised on the basis of their action and function as either non-cross-linking adducts and cross-linking adducts such as hydroimidazoles (Bohlender, Franke et al. 2005). Some of the best characterised AGEs to date, include N-carboxymethyllysine (CML), N-carboxyethyllysine (CEL), pentosidine, imidazole, glyoxallysine dimer (GOLD) and pyrraline (Brownlee 1992; Schrijvers, De Vriese et al. 2004; Wolf 2004; Bohlender, Franke et al. 2005). In addition, there are a number of exogenous sources of AGEs identified in recent times, including food and tobacco smoke, which also contribute to the body's AGE pool (Cerami, Founds et al. 1997; Koschinsky, He et al. 1997).

Under normal physiological conditions, AGEs are cleared from the body via the kidney, following their degradation by reductase enzymes within cells such as macrophages. The kidney via a multi-step process, filters AGE modified-peptides and proteins. Following filtration via the glomeruli, they are subsequently reabsorbed by the proximal tubules where they are often further degraded and then excreted into the urine (Kalousova, Zima et al. 2004). In homeostasis, the rate of renal AGE removal is proportional to creatinine clearance, ensuring that there is no excess accumulation of tissue AGEs.

In metabolic disorders, such as diabetes, there is a marked increase in a number of factors which promote the formation and accumulation of AGEs within various susceptible organs, in particular, the kidney. As a direct result of the hyperglycaemia characteristic of diabetes, there is marked increase in both carbonyl and oxidative stress, which each promote in vivo AGE accumulation (Miyata, Haneda et al. 1996; Miyata and van Ypersele de Strihou 2003).

Excessive AGE accumulation can elicit a variety of deleterious effects on tissues and organs. These include altering the structure and function of both intracellular and extracellular molecules, increasing oxidative stress, modulation of cell activation, enhancement of signal transduction pathways and increasing the activation and expression of cytokines and growth factors. These actions have been shown to be mediated via both receptor dependant and independent mechanisms (Brownlee 1995; Schrijvers, De Vriese et al. 2004 Circulating levels of AGEs in diabetic patients are elevated with decreased renal function {Kubba, 2003 #916). Furthermore, AGE accumulation in tissues correlate with the severity of organ injury, particularly within glomerular lesions (Shimoike, Inoguchi et al. 2000; Kanauchi, Nishioka et al. 2001).

Dietary AGEs, are also thought to contribute to the development of diabetic nephropathy. Diets low in AGE content, when fed to non-obese diabetic mice (type 1) and db/db mice (type 2) reduced glomerular lesions, creatinine/albumin ratios and renal TGFβ1 expression when compared to their high AGE counterparts (Zheng, He et al. 2002). Moreover, diets high in AGE content are known to impair insulin sensitivity further confounding downstream complications (Hofmann, Dong et al. 2002). Harcourt et al, have recently demonstrated the benefits of low AGE diets on kidney function in pre-diabetic, obese individuals. Diets low in AGE content elicited improvements in renal function and reduction in inflammation (Harcourt, Sourris et al.). Various agents, including LR-90 (Figarola, Scott et al. 2003), aminoguanidine (Youssef, Nguyen et al. 1999), and ALT-711 (Forbes, Thallas et al. 2003) are potent in reducing AGE accumulation in renal tissues in experimental diabetic nephropathy, subsequently improving renal function. Many other agents have elicited similar benefits and have been extensively reviewed previously (Alderson, Chachich et al. 2004; Williams and Tuttle 2005; Williams 2006). In addition, pyridoxamine, an intermediate of vitamin B_6, attenuated the progression of human diabetic nephropathy and concurrently reduced AGE and urinary TGF-β(Williams, Bolton et al. 2007). Furthermore, benfotiamine (liposoluble vitamin B1 derivative), decreases AGE accumulation, inflammation and improves vascular function in type 2 diabetic patients consuming diets high in AGE content (Stirban, Negrean et al. 2006). To date there have been three clinical trials conducted which employed AGE-lowering therapies . Aminoguanidine and benfotiamine trials were stopped due to toxicity of the therapy. The third trial employed Alagaebrium in type 1 diabetic patients in addition to an ACE-inhibitor. This trial has now ended and results are pending.

5.4 AGE-receptors

The receptors for AGE are important modulators of the deleterious effects of these compounds. Receptors for AGEs may be loosely grouped as either inflammatory (RAGE, AGE-R2) or clearance type receptors (AGE-R1, AGE-R3, CD36, Scr-II, FEEL-1 and FEEL-2) (Vlassara and Bucala 1996; Vlassara 1997; Singh, Barden et al. 2001; Forbes, Yee et al. 2004; Schrijvers, De Vriese et al. 2004; Alikhani, Alikhani et al. 2005). Vascular, renal, neuronal and

haematopoietic cells are all known to express receptors for AGEs (Goldin, Beckman et al. 2006; Sourris and Forbes 2009) AGEs contribute to the pathogenesis of diabetic nephropathy via receptor mediated mechanisms and indirectly via the generation of reactive oxygen species and by altering extracellular matrix (ECM) integrity.

Diabetes alters the expression of a number of AGE-receptors thought to drive the development and progression of diabetic nephropathy, in particular, the expression of RAGE on cells such as podocytes and tubular epithelial cells (Soulis, Thallas et al. 1997; Wendt, Tanji et al. 2003; Gu, Hagiwara et al. 2006; Li, Nakamura et al. 2006).

Another AGE receptor postulated to be involved in the development of diabetic nephropathy is AGE-R1, although converse to RAGE this is likely via a decrease in expression. In an experimental model of type 1 diabetes, renal AGE-R1 expression is reduced in association with a concurrent increase in AGE deposition and progression to diabetic nephropathy (He, Zheng et al. 2000; Vlassara 2001). In addition, we recently reported that in a small cohort of type 2 diabetic patients we found a positive correlation with AGE-R1 expression on the cell surface of peripheral blood mononuclear cells and renal function. We found that this was the most predictive biomarker for renal function and further investigation in a larger cohort is required {Sourris, #9145}.

The contribution of AGE-R3 to the development and progression of diabetic nephropathy has not been extensively researched. However, AGE-induced increases in the expression of AGE-R3 has been demonstrated in cultured endothelial cells and within renal tissues in the diabetic milieu (Iacobini, Oddi et al. 2005; Kumar, Narang et al. 2006). This however, may indicate a protective role for AGE-R3 given that AGE-R3 deficient mice develop more severe renal disease and have marked increases in renal AGE deposition (Iacobini, Oddi et al. 2005). Furthermore, AGE-R3 deficient mice develop albuminuria, mesangial expansion and fibrosis within the kidney cortex which is more pronounced with diabetes. Importantly, the deletion of AGE-R3 was also associated with a decrease in AGE-R1 and increased expression of RAGE demonstrating the existence of AGE-receptor cross talk. This study highlights that the role of AGE-R3 in the clearance of AGEs (Pugliese, Pricci et al. 2000) is likely more important in diabetic nephropathy than its ability to modulate immune function. The modulation of AGEs and their receptors have been extensively reviewed previously (Sourris and Forbes 2009).

6. Hyperlipidaemia

Hyperlipidaemia is a comorbidity often seen in diabetic patients and is thought to be an important contributor to progressive micro and macrovascular complications. This is most clearly demonstrated by the renoprotection which is seemingly afforded with HMG CoA reductase inhibitors (Tonolo, Ciccarese et al. 1997; Fujii, Inoguchi et al. 2007; Matsumoto, Tanimoto et al. 2008). Obesity is one the leading factors which drive the development of type 2 diabetes and its complications such as nephropathy. Moreover, it has also been shown to lead to kidney disease in the absence of diabetes. As one of the leading causes of chronic kidney disease, the WHO has recommended that lifestyle changes such as dietary and exercise are the most cost-effective approaches to combating this epidemic. We have recently reported the benefits of dietary intervention and renal function in a obese, non-diabetic population (Harcourt, Sourris et al.).

7. Reactive oxygen species

Reactive oxygen species are important intermediates in the formation of AGEs and are often excessively generated in the kidney in diabetes (Forbes, Coughlan et al. 2008). In addition, concomitant dysregulation of anti-oxidant enzymes in diabetes, leads to a state of oxidative stress (Forbes, Coughlan et al. 2008). To date, it is unclear as to why exogenous administration of antioxidants *per se* has demonstrated such poor renoprotection in humans, despite exciting positive preclinical research findings. However, it seems evident that therapies such as vitamins may not be the ideal antioxidant strategy in human DN. Vitamin B6 derivatives (Hammes, Du et al. 2003; Endo, Nishiyama et al. 2007), metformin (Rahbar, Natarajan et al. 2000), OPB-9195 (Wada, Nishizawa et al. 2001; Mizutani, Ikeda et al. 2002), ACEi (Miyata, van Ypersele de Strihou et al. 2002; Coughlan, Thallas-Bonke et al. 2007), AT1 antagonists (Miyata, van Ypersele de Strihou et al. 2002), ALA (Coughlan, Thallas-Bonke et al. 2007) and sRAGE (Wautier, Zoukourian et al. 1996) have exhibited beneficial effects on excess superoxide generation within tissues, associated with improvements in the development and/or progression of diabetic complications.

Vitamin B-related therapeutics are effective scavengers of ROS intermediates. Pyridoxamine, inhibits superoxide radical generation, as well as preventing the progression of neuropathy and retinopathy (Jain and Lim 2001). In addition benfotiamine and thiamine, Vitamin B1 derivatives, have shown beneficial effects in normalising ROS production and reducing the activity of aldose reductase (Berrone, Beltramo et al. 2006). Paradoxically, thiamine administered to human with diabetic renal disease actually worsened renal function (Rabbani, Alam et al. 2009). The role of ROS in diabetic kidney disease has been extensively reviewed previously (Forbes, Coughlan et al. 2008).

8. Inhibition of protein kinase C (PKC) activity

There has been a growing body of evidence suggesting the central role of PKC, which is broadly involved in signal transduction from the plasma membrane to the nucleus, in diabetes induced vascular dysfunction (Inoguchi, Battan et al. 1992; Xia, Inoguchi et al. 1994). PKC has 11 different isoforms, many of which have been shown to be involved in diabetic complications, in particular nephropathy. (Koya, Jirousek et al. 1997; Koya, Haneda et al. 2000; Meier, Park et al. 2003). Of the 11 isoforms, PKC-α, -β, -δ, -ε, -ξ are expressed within the kidney (Kanwar, Sun et al.) PKC pathway is known to be activated by many factors including: Elevations in diacylglycerol, hydrogen peroxide, increased activity of polyol pathway, mitochondrial superoxide activity (Geraldes and King) and following AGE-RAGE interactions (Kanwar, Sun et al.). PKC isoforms have been associated with many cellular and vascular alterations and processes including: endothelial dysfunction, angiogenesis, vascular permeability, cell growth and apoptosis, basement membrane thickening, extracellular matrix (ECM) expansion. PKC pathway is known to be activation of numerous cellular pathways including NADH, ROS, Na^+/K^+ ATPase , Endothelin (ET-1), Ang II, MAPK and phospolipase A2 and VEGF (Geraldes and King; Kanwar, Sun et al.).

We have recently reported the attenuation of PKC-α phosphorylation and translocation with ALA in both *in vivo* models of DN and *in vitro* studies (Thallas-Bonke, Lindschau et al. 2004). It remains to be determined if this action of alagebrium on PKCα phosphorylation partly explains its renoprotective actions. Modulation of PKC activity within the diabetic kidney has also been exhibited by various vitamin B derivatives (Babaei-Jadidi, Karachalias et al.

2003; Hammes, Du et al. 2003). Interestingly, both ACEi and aminoguanidine prevent diabetes associated increases in PKC β activation in renal glomeruli (Osicka, Yu et al. 2000). The effects of aminoguanidine and ACEi on PKC β activity were also observed at other sites of vascular injury including the retina and mesenteric vascular bed (Osicka, Kiriazis et al. 2001; Miyata, van Ypersele de Strihou et al. 2002). In addition, AT-1 receptor antagonists, also attenuate diabetes induced increases in PKC -epsilon activity within the diabetic heart (Malhotra, Reich et al. 1997). Furthermore, modulation of PKC has been demonstrated in vascular endothelial cells with the insulin sensitizing agent metformin (Isoda, Young et al. 2006) and the anti-thrombotic therapeutic, aspirin (Dragomir, Manduteanu et al. 2004). We have demonstrated that in our experimental models of diabetes translocation of PKC α to the membrane is associated with parallel increases in superoxide production and elevated urinary VEGF thus highlighting the importance of this pathway in DN. In the clinical setting, roboxistaurin, is a PKC inhibitor which Tuttle et al, demonstrated that 32mg/day in addition to an ACEi for 12 months reduced urinary ACR (Geraldes and King). Moreover, renal biopsies from diabetic patients exhibited almost 10-fold increase in PKC β gene expression compared to their control (Geraldes and King; Langham, Kelly et al. 2008). In addition, the importance of PCK isoforms has been demonstrated in experimental models of diabetic nephropathy. PCK-α and β knockout mice exhibited a high level of resistance to the development of diabetic renal disease (Meier, Park et al. 2007; Meier, Menne et al. 2009; Tossidou, Starker et al. 2009).

9. Nuclear transcription factor kappa-B (NF-κB)

NF-κB is a transcription factor composed of two subunits, the most common of which are the p50 and p65 subunits (Barnes and Larin 1997) which are thought to be important modulators of diabetic complications. The active p65 subunit in particular, is thought to be central in the activation of numerous genes including cytokines, adhesion molecules, NO synthase, angiotensinogen and many other inflammatory and proliferative proteins implicated in the process of diabetic nephropathy (Barnes and Larin 1997; Bierhaus, Schiekofer et al. 2001). NF-κB is activated by a range of stimuli including glucose (Pieper and Riazulhaq 1997) and ROS (Nishikawa, Edelstein et al. 2000). AGEs are also involved in activation of NF-κB via a RAGE-dependent pathway leading to its translocation to the nucleus where it induces transcription of target genes such as IL-6 and TNF-α (Yan, Schmidt et al. 1994). The diverse actions of NF-κB and the capacity of various factors such as AII and AGEs to activate this transcription factor (Ruiz-Ortega, Lorenzo et al. 2000; Ruiz-Ortega, Lorenzo et al. 2000), are consistent with NF-κB playing a pivotal role in the pathogenesis of diabetic complications.

Pyrrolidine dithiocarbamate (PDTC) is a NF-κB inhibitor which has been used in both diabetic (Lee, Cao et al. 2004) and non-diabetic animal models of renal disease where it is renoprotective (Rangan, Wang et al. 1999), although its toxicity does not allow for direct translation to the clinical setting. Indeed, our group has demonstrated the importance of NF-κB in the pathogenesis of early renal macrophage infiltration in experimental diabetes, which could be modulated by interruption of the RAS (Lee, Cao et al. 2004; Liu, Wei et al. 2006). Moreover, diabetes-induced increases in NF-κB activation are prevented by numerous therapeutics including Metformin (Isoda, Young et al. 2006) aspirin (Zheng, Howell et al. 2007) Vitamin B derivatives (Hammes, Du et al. 2003) carnosine (Odashima,

Otaka et al. 2006) and thiazolidinediones (Marx, Walcher et al. 2004). It is possible that NF-κB, like PKC, is a central mediator which drives the downstream pathogenic consequences of interactions between hemodynamic and glucose dependent pathways in diabetic vascular complications. However, approaches to inhibit NF-κB have not been explored fully in DN, most likely due to the intimate involvement of this transcription factor in a number of essential cellular processes including apoptosis.

10. Inflammatory cytokines and growth factors

Diabetic nephropathy was not traditionally considered to be an inflammatory condition, however, there is a growing body of evidence in recent times highlighting the central role of inflammation in its development and progression (Wu, Huang et al. 2002; Forbes, Cooper et al. 2003; Chow, Ozols et al. 2004; Chow, Nikolic-Paterson et al. 2004; Chow, Nikolic-Paterson et al. 2006; Nguyen, Ping et al. 2006; Chow, Nikolic-Paterson et al. 2007; Ninichuk, Khandoga et al. 2007; Giunti, Tesch et al. 2008; Hohenstein, Hugo et al. 2008). Indeed, both hemodynamic and metabolic factors involved in the development of diabetic complications such as nephropathy activate common downstream targets, including cytokines and growth factors (Cooper, Gilbert et al. 1998). In particular, Monocyte Chemoattractant Protein (MCP-1), Transforming Growth Factor-β1 (TGF-β1), Connective Tissue Growth Factor (cTGF) and Vascular Endothelial Growth Factor (VEGF) have all been implicated in both experimental and human studies to be involved in the development and progression of diabetic nephropathy.

10.1 Monoctye chemoattractant protein -1 (MCP-1)

MCP-1 is a potent chemokine which encourages monocyte/macrophage infiltration into the kidney, which likely contributes to the progression of DN. MCP-1 production and secretion from damaged renal cells in diabetes are postulated to be a response to hyperglycaemia subsequently activating a number of signalling pathways including those mediated by PKC and NF-κB (Tesch 2008). In an experimental model of type 2 diabetic nephropathy, a deficiency in MCP-1 resulted in a significant reduction in renal inflammatory infiltration and renoprotection, Furthermore administration of propagermanium, an antagonist of the MCP-1 receptor, in model of diabetic nephropathy, resulted in reduced renal hypertrophy and macrophage infiltration in renal glomeruli (Kanamori, Matsubara et al. 2007). Indeed, it has been demonstrated that elevations in urinary excretion of MCP-1 may be a valid diagnostic marker of diabetic nephropathy in type 2 diabetic patients (Wang and Chen 2009). These studies suggest that MCP-1 is a central mediator of diabetic renal disease, although its utility as a therapeutic target remains to be determined (Chow, Nikolic-Paterson et al. 2007).

10.2 Modulation of growth factors

Growth factors such as transforming growth factor-β (TGF-β), a fibrogenic cytokine, and connective tissue growth factor (CTGF), which is primarily induced by TGF- β1, have been implicated as key effector molecules which promote diabetic renal disease. Transforming growth factor beta is a superfamily with three mammalian isoforms. The major isoform, TGF-β1 is synthesised as an inactive or latent form, which subsequently is subjected to proteolytic cleavage leading to the generation of the active form. TGF-β1 binds to the type II receptor and subsequently binds to the type I receptor (Wrana, Attisano et al. 1994) inducing

phosphorylation and intracellular signalling involving the SMAD proteins (Massague 1998). In vitro studies have shown that a range of stimuli increase TGF-β1 expression including hyperglycaemia, AGEs, stretch, AII, endothelin, lipids and various products of oxidative stress such as F_2 isoprostanes, all factors relevant to DN (Rocco, Neilson et al. 1992; Wolf, Ziyadeh et al. 1995; Herman, Emancipator et al. 1998; Gruden, Thomas et al. 1999; Jandeleit-Dahm, Cao et al. 1999; Montero, Munger et al. 2000). Ziyadeh *et al* have previously examined the effects of long-term administration of a neutralizing TGF-β1 antibody on renal function and structure in diabetic *db/db* mice (Ziyadeh, Hoffman et al. 2000) and STZ diabetic mice (Sharma, Jin et al. 1996). Although most of the benefits have been attributed to TGF-β1, Hill *et al*. have suggested that another isoform, TGF-β2, is closely linked to fibrogenesis in diabetic nephropathy (Hill, Flyvbjerg et al. 2000). The utility of TGF-β1 as a target for therapeutic intervention in DN, however, is impeded by its essential role in inflammatory and immune processes. Therefore it may be preferable to modulate renal TGF-β1 levels by an alternative approach such as therapies which focus on upstream advanced glycation pathways. A clinical trial in type 2 diabetic patients has recently ended and reports have been released. In this study by Sharma et al, they employed the anti-fibrotic therapeutic, Pirfenidone at two different doses to investigate the benefits on renal function. Administration of Perfenidone at the lower dose of 1200mg resulted in a concurrent improvement in renal function and reduction in TGF-β thus demonstrating its benefits as a potential therapeutic for diabetic nephropathy (Sharma, Ix et al.).

10.3 Connective tissue growth factor

Another pro-sclerotic cytokine, connective tissue growth factor (CTGF) has increased renal (Riser, Denichilo et al. 2000; Twigg, Cao et al. 2002) and in particular, glomerular expression in diabetes (Murphy, Godson et al. 1999; Riser, Denichilo et al. 2000) and elevated in both early and late diabetic nephropathy in humans (Ito, Aten et al. 1998). Currently a Phase II study of FG-3019, a humanised anti-CTGF antibody, has been completed in patients with diabetic nephropathy (microalbuminuria) which was well tolerated and improved albuminuria. Subsequent, studies are planned in diabetic patients with macroalbuminuria (http://www.fibrogen.com/trials).

CTGF expression is thought to be mediated by a number of factors common in diabetic nephropathy including TGF-β1, hyperglycaemia or mechanical stretch (Riser, Denichilo et al. 2000). Interestingly, AGEs have been reported to specifically increase CTGF expression, initially in fibroblasts (Twigg, Chen et al. 2001) but subsequently in mesangial cells (Twigg, Chen et al. 2001). Moreover, aspirin has also been shown to prevent the diabetes-mediated increase in CTGF and mesangial expansion in experimental models of DN (Makino, Mukoyama et al. 2003).

10.4 Vascular endothelial growth factor (VEGF)

Vascular endothelial growth factor (VEGF) is a cytokine whose major role in diabetes was initially considered to be central for the pathogenesis of diabetic retinopathy and in particular retinal neovascularisation. Recent findings, however, have demonstrated the importance of VEGF within the diabetic kidney (De Vriese, Tilton et al. 2001; Wada, Nishizawa et al. 2001; Rizkalla, Forbes et al. 2003; Wendt, Tanji et al. 2003; Thallas-Bonke, Lindschau et al. 2004)]. We and others have previously shown both in vivo and in vitro decreases in VEGF expression with a number of therapies including alagebrium (Thallas-

Bonke, Lindschau et al. 2004), ACE inhibitors (Thallas-Bonke, Lindschau et al. 2004), sRAGE (Wendt, Tanji et al. 2003) and OPB-9195 (Wada, Nishizawa et al. 2001). Despite this suppression of VEGF as a result of current therapeutics, the benefits of VEGF suppression remain controversial with some studies suggesting that VEGF blockade is renoprotective (De Vriese, Tilton et al. 2001), whereas recent studies, albeit in a non-diabetic context, suggest that VEGF is a critical renal survival factor and that blockade may in fact promote renal damage (Advani, Kelly et al. 2007). This is perhaps best demonstrated by the differential effects seen with anti-VEGF antibodies (192,193). Studies on the renal effects of blockade of VEGF receptor (VEGFR) signalling are currently being performed. Indeed, a recent preliminary report has shown that SU5416, a VEGFR tyrosine kinase inhibitor, reduces albuminuria in *db/db* mice (Sung 2004). In experimental models of DN, VEGF expression is also decreased by an inhibitor of AGE formation (Tsuchida, Makita et al. 1999) and with the AGE cross-link breaker, ALA (Thallas-Bonke, Lindschau et al. 2004) further confirming the link between AGEs and VEGF expression.

11. Targeting genetic mediators of diabetic nephropathy

Whilst, genetic factors and gene mutations have been implicated in the development and pathogenesis of diabetes for some time, recent evidence has implicated the involvement of , microRNA's, histone methylation and metabolic memory in diabetes and specifically its complications.

11.1 MicroRNAs (miRNAs)

MiRNAs are regulatory RNAs that act as post-transcriptional repressors by binding to the 3'untranslated region of target genes (Akkina and Becker; Guay, Roggli et al.). The mammalian genome encodes for several hundred miRNAs, and within the kidney, the miRNA profile differs from that of other tissues and indeed within different compartments of the kidney (Akkina and Becker; Guay, Roggli et al.). Initially miRNAs are transcribed as long pre-miRNA molecules which are subsequently modified to become their mature miRNA form, approximately 19-25 nucleotides in length, via a number of different processes. A strand of mature miRNA enters the RNA-inducing silencing complex (RISC) where it binds to the 3' untranslated region of its target mRNA thus resulting in reduced expression of the targeted gene (Akkina and Becker) The miRNA which are in greatest abundance within the kidney include: miR-192, 194, 204, 215 and 216. Kantharidis et al have demonstrated in-vitro and ex-vivo potential of miRNA as therapeutic targets in diabetic nephropathy. Specifically, they have demonstrated the role of microRNA's in the fibrosis associated with diabetic nephropathy. MicroRNA-192/215 was found to regulate the pro-fibrotic protein e-cadherin whilst miRNA-200a was found to repress the expression of TGF-ß2 (Wang, Herman-Edelstein et al.; Wang, Koh et al.) Natarajan et al have alos extensively investigated microRNA in diabetic renal disease in experimental models (Kato, Arce et al.; Kato, Arce et al. 2009; Kato and Natarajan 2009; Kato, Putta et al. 2009). This therefore highlights the potential of microRNA's as therapeutic targets for diabetic nephropathy and further pre-clinical work is warranted.

11.2 Metabolic memory

A number of pre-clinical and clinical trials have implicated the involvement of metabolic memory and the development of diabetic complications. Metabolic memory refers to an

earlier hyperglycaemic or erratic metabolic controlled state which is then followed by "normoglycaemia" or good glycaemia control. This phenomenon is poorly understood, however it suggests that despite improved glycemic control, the original exposure to hyperglycaemia is enough to sustain prolonged deleterious effects and outcomes. Metabolic memory has been demonstrated in both experimental and cell culture models of diabetes. In addition, numerous clinical trials, including the United Kingdom Prospective Diabetes Study (UKPDS) and The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) demonstrated that intensive glycaemia control may help decrease micro and macrovasuclar complications thus suggesting the existence of metabolic memory (Villeneuve and Natarajan). Brassacchio et al have demonstrated the existence of "hyperglycaemic memory" in an in-vitro model of diabetes (Brasacchio, Okabe et al. 2009) however further investigation into this phenomenon is warranted and would undoubtedly reduce the onset and progression of diabetic complications, including nephropathy.

11.3 Histone modifications

Post-translational modifications that occur at the histone tails including: acetylation, methylation, and phosphorylation, one of the many methods through which regulation of gene transcription is achieved. Traditionally, post-translational modifications, such as DNA methylation have been extensively studied in the area of cancer. Recent reports have demonstrated the importance of histone modifications in diabetic complications. Pre-clinical studies in white blood cells including monocytes from diabetic patients have exhibited epigenetic modifications including increases in H3K9me2 AND H3K4me2 which are associated with immune and inflammatory pathways (Villeneuve and Natarajan). In addition, TGF- ß treatment of renal mesangial cells were found to induce an increase in HMT SET7/9 which was associated with a profibrotic phenotype (Villeneuve and Natarajan). Histone modifications therefore demonstrate great potential as therapeutic targets.

12. Clinical trials: The current state of affairs

It is clearly evident that there is an abundance of potential therapeutic targets for the treatment of diabetic nephropathy. So why are we failing to translate these into positive outcomes in patients? We investigated the NIH database for clinical trials (completed and running) which targeted diabetic nephropathy. Of the 200 trials listed in the database, we categorised the interventions into their broad subject groups (Table 1). Our search found that 35% of all trials, employed interventional therapies which targeted the renin-aldosterone-angiotensin system, which to date have proven to be the most beneficial therapeutic approach (Table 1). Approximately 13.5% of all clinical trials were investigating therapies which target glycaemic control (including insulin). Dietary intervention is a more cost effective therapeutic approach for the treatment of diabetic nephropathy constituted some 20% of all clinical trials registered within the NIH data base. It is evident that the wider research community is actively investigating novel therapeutic targets other than those which target the RAAS, demonstrated by the variety of interventions and categories. Of particular interest, is that of all of these trials, almost 10% of these targeted ROS whilst 5% employed anti-inflammatories. In addition, 1.5% of all trials targeted AGEs and/or their receptors (Table 1). The remainder of the trials targeted thrombosis, fibrosis, erythropoiesis,

heparin, PKC, calcium transport, endothelin and genetics (Table 1). A recent search into the diabetic nephropathy patent database has identified that other new novel therapeutics including vasohibin (20100113354), myostatin (20110008357), Oligotide (20100291098), modulators of prostacyclin (20110053872), inhibitors of galectin-3 (20080219973) and inhibitors of fatty acid oxidation (20110048980) are being considered for the treatment of diabetic renal disease. Moreover, novel biomarkers for the development and progression of diabetic nephropathy are also under investigation including urinary: precursor α-2-HS-glycoprotein, α-1-antitrypsin, α-1-acid glycoprotein and osteopontin.

TARGET	PERCENTAGE
Glycaemic Control (including insulin and glucose transport)	14.5%
Advanced Glycation End-Products	1.5%
Reactive Oxygen Species	9%
Inflammation	5%
Renin-aldosterone-angiotensin system	35%
Endothelin	2.5%
Dietary Interventions	17.5%
Pro-fibrotic molecules	2%
Anti-Thrombotic	1.5%
Genetics	1%
Protein Kinase C- inhibitors	1%
Anti-Lipidaemic	4.5%
Calcium Blockers	1.5%
Others – diuretics, hormones, apoptosis,	5%

Table 1. Therapeutics in clinical trials for treatment of diabetic nephropathy Representative table of Clinical Trials run to treat diabetic nephropathy and registered on NIH webpage.

13. Conclusion

Diabetic nephropathy is a multifaceted disease which encompasses hemodynamic, metabolic and genetic factors which are central to its development and progression. At present therapeutics which target the hemodynamic factors, specifically the renin-aldosterone-angiotensin system are the most effective treatments. Unfortunately, their benefits are limited and as such additional novel therapeutics are required. In this chapter we have described an number of potential therapeutic targets which have been identified and which are either in clinical or pre-clinical investigation. In the future, it is hoped that current clinical trials will show benefits of some of these novel agents and that there will be significant advanced in our management of individuals with diabetic renal disease.

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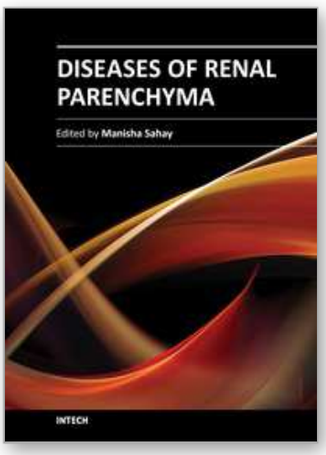

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Clinical nephrology is an evolving speciality in which the amount of information is growing daily. This book gives quick access to some important clinical conditions encountered in nephrology including the diseases of glomeruli, tubules and interstitium. It presents the latest information on pathophysiology, diagnosis and management of important diseases of renal parenchyma. The information is presented in a very user friendly and accessible manner while the treatment algorithms enable the reader to quickly access expert advice on arriving at the most appropriate treatment regimen. The book discusses the renal involvement in various systemic diseases including diabetes and autoimmune diseases. Diabetic nephropathy is fast becoming the commonest cause of end stage renal disease all over the globe and is discussed in this book. The editors believe that this book will be a valuable addition to the reader's library.

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