Molecular Mechanisms of Diabetic Nephropathy and Its Therapeutic Intervention

Sho-ichi Yamagishi[1,*], Kei Fukami[2], Seiji Ueda[2] and Seiya Okuda[2]

Departments of Medicine, [1]Division of Caridovascular Medicine and [2]Nephrology, Kurume University School of Medicine, Kurume 830-0011, Japan

Abstract: Diabetic nephropathy is a leading cause of end-stage renal failure, which could account for disabilities and high mortality rates in patients with diabetes. Diabetic nephropathy seems to occur as a result of an interaction between metabolic and hemodynamic factors, which activate common pathways that lead to renal damage. Recent large landmark clinical studies have shown that intensive glucose control reduces the risk of the development and progression of diabetic nephropathy, and the blockade renin-angiotensin system (RAS) is also an important target for both metabolic and hemodynamic derangements in diabetic nephropathy. However, diabetic nephropathy remains the leading cause of end-stage renal failure in developed countries. Therefore, to develop novel therapeutic strategies that specifically target diabetic nephropathy may be helpful for most patients with diabetes. High glucose, *via* various mechanisms such as increased production of oxidative stress and advanced glycation end products (AGEs), and activation of the RAS and protein kinase C (PKC), elicits vascular inflammation and alters gene expression of growth factors and cytokines, thereby it might be involved in the development and progression of diabetic nephropathy. This article summarizes the molecular mechanisms of diabetic nephropathy and the potential therapeutic interventions that may prevent this devastating disorder even in the presence of hyperglycemia, control of which is often difficult with current therapeutic options.

Key Words: Diabetic nephropathy, AGEs, oxidative stress, PKC, renin-angiotensin system.

INTRODUCTION

Diabetes mellitus has been increasing global health problem affecting more than 170 million people worldwide by 2000. According to the World Health Organization, it is expected that the number of diabetic people will rise to 370 million by 2030 in the world [1]. It has been considered that about 25-40% of patients with type 1 or type 2 diabetes develop nephropathy within 20-25 years of the onset of disease [2]. Therefore, diabetic nephropathy is now becoming a devastating disorder, which could account for significant morbidity and mortality in Western world [3]. The major clinical treatment targets for diabetic nephropathy are hyperglycemia and hypertension. Indeed, recent large prospective clinical studies including Diabetes Control and Complication Trial (DCCT) [4] and the UK Prospective Diabetes Study (UKPDS) [5] have shown that intensive glucose or blood pressure control reduces significantly the risk for the development and progression of diabetic nephropathy, and recently, the blockade of the renin-angiotensin system (RAS) is reported to be efficacious against the progression of renal damage in type 1 and type 2 diabetic patients [6]. However, diabetic nephropathy remains the leading cause of end-stage renal disease (ESRD) in developed countries. Accordingly, to develop novel therapeutic strategies that speci-fically target diabetic nephropathy may be helpful for most patients with diabetes.

*Address correspondence to this author at the Department of Medicine, Division of Caridovascular Medicine, Kurume University School of Medicine, Kurume 830-0011, Japan; Tel: +81-942-31-7580; Fax: +81-942-31-7707; E-mail: shoichi@med.kurume-u.ac.jp

Chronic hyperglycemia is a major initiator of diabetic nephropathy. Various hyperglycemia-induced metabolic and hemodynamic derangements, including increased advanced glycation end product (AGE) formation, enhanced production of reactive oxygen species (ROS), and activation of protein kinase C (PKC) and the RAS, contribute to the characteristic histopa-thological changes observed in diabetic nephropathy [7]. This review summarizes the molecular mechanisms of diabetic nephropathy and the potential therapeutic interventions that may prevent it even in the presence of hyperglycemia.

Pathophysiology of Diabetic Nephropathy

The earliest clinical evidence for incipient diabetic nephropathy is the development of the persistent microalbuminuria (urinary albumin excretion rate (UAER), 20-200 μg/min), which is Albustix-negative. The natural history of diabetic nephropathy differs between type 1 and type 2 patients [8]. If untreated, approximately 80 % of type 1 diabetic patients will develop overt albuminuria (UAER>200 μg/min) over a 15-year period. Of these patients, 50 % will develop ESRD over the ensuring 10 years. In type 2 diabetes, if no treatment is initiated, up to 20-40 % of patients will progress to overt albuminuria and 20 % of those with overt albuminuria will develop ESRD over the next 20 years. When comparing two types of diabetes, diabetic nephropathy is less common (5-10 %) in type 2 diabetes than in type 1 diabetes (30-40 %) although the total number of patients with ESRD is similar for the two diabetic populations.

Diabetic nephropathy is a leading cause of ESRD, and accounts for disabilities and the high mortality rate in pa-

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tients with diabetes [9, 10]. Development of diabetic nephropathy is characterized by glomerular hyperfiltration and thickening of glomerular basement membranes, followed by an expansion of extracellular matrix in mesangial areas and increased UAER. Diabetic nephropathy ultimately progresses to glomerular sclerosis associated with renal dysfunction [11]. Further, it has recently been recognized that changes within tubulointerstitium, including proximal tubular cell atrophy and tubulointerstitial fibrosis, are also important in terms of renal prognosis in diabetic nephropathy [12-16]. Such tubular changes have been reported to be the dominant lesion in about one third of patients with type 2 diabetes [17]. It appears that both metabolic and hemodynamic factors interact to stimulate the expression of cytokines and growth factors in glomeruli and tubules from the diabetic kidney [18].

Numerous studies have demonstrated that the RAS is an important target for both metabolic and hemodynamic pathways in diabetic nephropathy. So far, angiotensin-converting enzyme inhibitors (ACE-Is) and an angiotensin II (Ang II) type I receptor blockers (ARBs) have been widely used as major therapeutic agents for diabetic nephropathy in both type 1 and type 2 diabetic patients [19-21]. The renoprotective effects of these agents are largely ascribed to its blood pressure (BP)-lowering properties, however, a recent clinical study suggests the pleiotropic effects of the RAS inhibitors, *that is*, beyond BP-lowering effects, on diabetic nephropathy. Indeed, it has been shown that irbesartan, an ARB, significantly prevents the progression of diabetic nephropathy in type 2 diabetic patients, compared with a calcium channel blocker, amlodipine, with an equipotent BP-lowering property [22]. Further, the RAS stimulates the production of several growth factors and cytokines [23]. The deleterious actions of Ang II on diabetic nephropathy are mediated partly by transforming growth factor-β (TGF-β), a fibrogenic factor [24-26]. In addition, other factors such as connective tissue growth factor (CTGF), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) in relation to intracellular second messenger molecules such as mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-κB) and PKC, have also been linked to the RAS, thereby implicated in the development and progression of diabetic nephropathy [23, 27-32]. It is also reported that high glucose, *via* various mechanisms such as increased production of oxidative stress and AGEs, activates the RAS, being involved in diabetic nephropathy as well [33].

Molecular Mechanisms of Diabetic Nephropathy and the Therapeutic Interventions

(1) AGEs

AGEs induce apoptotic cell death and VEGF expression in human cultured mesangial cells [34]. Mesangial cells occupy a central anatomical position in the glomerulus, playing crucial roles in maintaining structure and function of glomerular capillary tufts [34]. They actually provide structural support for capillary loops and modulate glomerular filtration by its smooth muscle activity [35]. Therefore, it is conceivable that the AGE-induced mesangial apoptosis and dysfuction may contribute in part to glomerular hyperfiltration, an early renal dysfunction in diabetes [34]. Several experimental and clinical studies support the pathological role for VEGF in diabetic nephropathy. Indeed, antibodies raised against VEGF have been reported to improve hyperfiltration and albuminuria in streptozotocin-induced diabetic rats [36]. Inhibition of VEGF also prevents glomerular hypertrophy in a model of obese type 2 diabetes, the Zucker diabetic fatty rat [37]. Further, urinary VEGF levels are positively correlated with the urinary albumin to creatinine ratio, and negatively correlated with creatinine clearance in type 2 diabetic patients [38]. These observations suggest that urinary VEGF might be used as a sensitive marker of diabetic nephropathy. VEGF overproduction elicited by AGEs may be involved in diabetic nephropathy.

Moreover, we have recently found that AGEs stimulate monocyte chemoattractant protein-1 (MCP-1) expression in mesangial cells as well [34]. Increased MCP-1 expression associated with monocyte infiltration in mesangium has been observed in the early phase of diabetic nephropathy [39]. Plasma MCP-1 was positively correlated with UAER in type 1 diabetic patients [40]. AGE accumulation in glomerulus could also be implicated in the initiation of diabetic nephropathy by promoting the secretion of MCP-1.

AGEs formation on extracellular matrix proteins alters both matrix-matrix and cell-matrix interactions, being involved in the pathogenesis of diabetic glomerulosclerosis. For example, non-enzymatic glycations of type IV collagen and laminin reduce their ability to interact with negatively charged proteoglycans, increasing vascular permeability to albumin [41]. Furthermore, AGEs formation on various types of matrix proteins impairs their degradation by matrix metalloproteinases, contributing to basement membrane thickening and mesangial expansion, hallmarks of diabetic nephropathy [42]. AGEs formed on the matrix components can trap and covalently cross-link with the extravasated plasma proteins such as lipoproteins, thereby exacerbating diabetic glomerulosclerosis [43].

AGEs stimulate insulin-like growth factor-I, -II, PDGF and TGF-β in mesangial cells, which in turn mediate production of type IV collagen, laminin and fibronectin [44]. AGEs induce TGF-β overexpression in both podocytes and proximal tubular cells as well [45,46]. Recently, Ziyadeh *et al.* reported that long-term treatment of type 2 diabetic model mice with blocking antibodies against TGF-β suppressed excess matrix gene expression, glomeru-losclerosis, and prevented the development of renal insufficiency [47]. These observations suggest that the AGE-induced TGF-β expression plays an important role in the pathogenesis of glomerulosclerosis and tubulointerstitial fibrosis in diabetic nephropathy.

In vivo, the administration of AGE-albumin to normal healthy mice for 4 weeks has been found to induce glomerular hypertrophy with overexpression of type IV collagen, laminin B1 and TGF-β genes [48]. Furthermore, chronic infusion of AGE-albumin to otherwise healthy rats leads to focal glomerulosclerosis, mesangial expansion, and albuminuria [49]. Recently, RAGE (receptor for AGEs)-overexpressing diabetic mice have been found to show progressive glomerulosclerosis with renal dysfunction, compared with diabetic littermates lacking the RAGE transgene [50]. Further, diabetic homozygous RAGE null mice failed to develop

significantly increased mesangial matrix expansion or thickening of the glomerular basement membrane [45]. Taken together, these findings suggest that the activation of AGE-RAGE axis contributes to expression of VEGF and enhanced attraction/activation of inflammatory cells in the diabetic glomerulus, thereby setting the stage for mesangial activation and TGF-β production; processes which converge to cause albuminuria and glomerulosclerosis. AGEs including glycoxidation or lipoxidation products such as N^{ε}-(carboxymethyl)lysine, pentosidine, malondialdehyde-lysine accumulate in the expanded mesangial matrix and thickened glomerular basement membranes of early diabetic nephropathy, and in nodular lesions of advanced disease, thus further suggesting the active involvement of AGEs for diabetic nephropathy [51].

Aminoguanidine is a prototype therapeutic agent for the prevention of AGE formation [52]. Aminoguanidine is introduced as a hydrazine reagent for trapping reactive carbonyls formed during the Maillard reaction, especially Amadori intermediates, thus impeding their conversion into AGEs. Aminoguanidine reacts not only extensively with Amadori carbonyl groups of glycated proteins but also with dicarbonyl compounds such as methylg-lyoxal, glyoxal, and 3-deoxyglucosone [52]. A number of studies have demonstrated that aminoguanidine decreased AGE accumulation and plasma protein trapping in the glomerular basement membrane [52-54]. In streptozocin-induced diabetic rats, aminoguanidine treatment for 32 weeks dramatically reduced the level of albumin excretion and prevented the development of mesangial expansion [53]. Furthermore, aminoguanidine treatment was found to prevent albuminuria in diabetic hypertensive rats without affecting BP [54]. Double-blinded, placebo-controlled, randomized clinical trials of aminoguanidine (Pimagedine^{R}) (ACTION; A Clinical Trial In Overt Nephropathy) were designed to evaluate the safety and efficacy of aminoguanidine in retarding the rate of progression of renal disease in patients with overt diabetic nephropathy. Pimagedine^{R} therapy reduced the 24-hour total urinary proteinuria and prevented the decrease in glomerular filtration rate in patients with type 1 diabetes [55]. However, the effects of Pimagedine^{R} on serum creatinine doubling were found not to be significant; serum creatinine doubled in 26% of the placebo-treated patients and in 20% of those who received Pimagedine ($p = 0.099$). This study is noteworthy in providing the first clinical proof of the concept that inhibiting AGE formation can result in a clinically important attenuation of the serious complication of diabetes. Reported side effects of aminoguanidine in clinical therapy were gastrointestinal disturbance, abnormalities in liver function tests, flu-like symptoms, and a rare vasculitis [55]. Further clinical trials of aminoguanidine were terminated due to its safety concern.

We have found that OPB-9195 ((±)-2-isopropylidene-hydra-zono-4-oxo-thiazolidine-5-ylacetanilide), a synthetic thiazolidine derivative and novel inhibitor of AGEs, prevented the progression of diabetic nephropathy by lowing serum concentrations of AGEs and their deposition of glomeruli in Otsuka-Long-Evans-Tokushima-Fatty rats, a type II diabetes mellitus model animal [56]. OPB-9195 was also found to retard the progression of diabetic nephropathy by blocking type IV collagen production and suppressing overproduction of two growth factors, TGF-β and VEGF [56].

Recently, Baynes and his colleagues reported that pyridoxamine inhibited the progression of renal disease, and decreased hyperlipidemia and apparent redox imbalances in diabetic rats [57]. Pyridoxamine and aminoguanidine had similar effects on parameters measured, supporting a mechanism of action involving AGE inhibition [57]. Pyridorin, which is announced by BioStratum, was recently granted Fast Track status by the FDA and is currently advancing through Phase IIb clinical trials for the treatment of diabetic nephropathy (http://www.clinicaltrials.gov/ct/show/-NCT00320060). KOWA pharmaceuticals also commenced phase II clinical studies with K-163 (pyridoxamine) in Japan (http://www.kowa.co.jp/eng/g/rd/pipeline.htm).

LR-90, a methylene bis (4,4'-[2-chlorophenylureido phenoxyi-sobutyric acid]), is a new AGE inhibitor whose action is thought to be similar to those seen with aminoguanidine and pyridoxamine [58]. This agent has a strong metal chelation, thus leading to the inhibition of the formation of glycoxidative-AGEs and their interaction with ROS [58]. Figarola *et al.* demonstrated that LR-90 prevented progression of diabetic nephropathy in streptozotocin-induced diabetic rats [58].

Benfotiamine is a novel antioxidant agent that reduces AGE accumulation in diabetes [59]. Among these agents, benfotiamine, a lipid-soluble thiamine derivative, may be the most promising one. Recent studies have demonstrated that benfotiamine is able to block major biochemical pathways implicated in the pathogenesis of diabetic complications, including the accumulation of AGEs [60]. Further, Thornalley *et al.* has also reported in streptozotocin-induced diabetic model that benfotiamine therapy increases transketolase expression in renal glomeruli, increases the conversion of triosephosphates to ribose-5-phosphate, and subsequently inhibits the development of microalbuminuria [61]. Since hyperglycemia-induced generation of triosephosphates elicits mitochondrial oxidative stress production and stimulates the formation of AGEs such as methylglyoxal, benfotiamine may prevent the progression of diabetic nephropathy *via* the increased conversion of triosephosphates to ribose-5-phosphate [62].

We posit an overall scheme concerning the possible involvement of AGEs in diabetic nephropathy (Fig. **1**).

(2) PKC

Diabetic glomerular hyperfiltration is likely to be the consequences of hyperglycemia-induced decreases in afferent arteriolar resistance, which could lead to glomerular hypertension [63,64]. Some of the vasoconstrictive actions of Ang II are mediated by PKC activity [65]. Diacylglycerol (DAG)-PKC pathway may enhance the action of Ang II in glomeruli, thus being involved in early diabetic nephropathy. Further, hyperglycemia-induced PKC activation regulates arachidonic acid release and eicosanoid production by mesangial cells [66]. Therefore, increases in vasodilatory prostanoids such as prostaglandin E_2 *via* PKC activation may also be involved in hyperfiltration in diabetic nephropathy. Haneda *et al.* provided the evidence that MAPK cascade, an important kinase cascade downstream to PKC, activated cy-

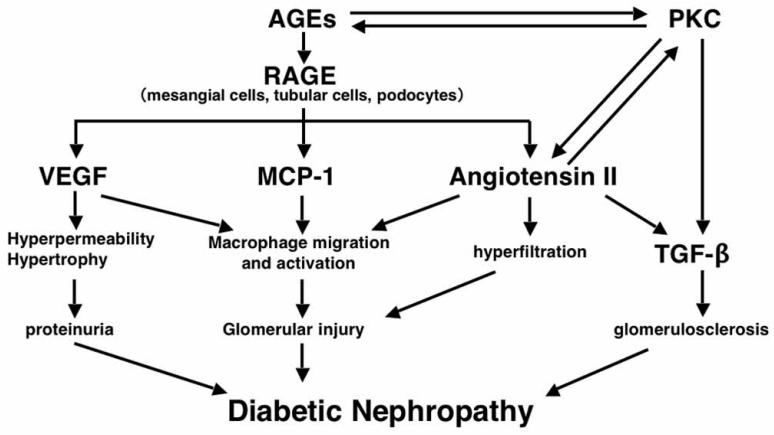

Fig. (1). Possible involvement of AGEs in diabetic nephropathy.

tosolic phospholipase A_2 by direct phosphorylation of this enzyme, in glomeruli isolated from streptozotocin-induced diabetic rats, thus contributing to the development of diabetic nephropathy [67].

PKC can increase extracellular matrix production in mesangial cells *via* TGF-β activation while PKC inhibitors prevent the hyperglucemia-induced increase in extracellular matrix and TGF-β expression in mesangial cells [68]. Recently, AGEs are reported to induce oxidative stress and activate PKC-β in neonatal mesangial cells, thus causing changes that may ultimately contribute to phenotypic abnormalities associated with diabetic nephropathy [69]. AGE-induced TGF-β overexpression in mesangial cells could be mediated by PKC activity.

In animal models of diabetes, including the streptozotocin rat, db/db mouse, and diabetic tranegenic mRen-2 rat models, an orally active PKC-β inhibitor LY333531, normalized glomerular hyperfiltration, decreased urinary albumin excretion, and reduced glomerular TGF-β and extracellular matrix protein production. As a result, mesangial expansion, glomerulosclerosis and tubulointers-titial fibrosis were significantly prevented with improvement of renal function [70-73].

(3) RAS

There is a growing body of evidence to suggest that that the RAS plays an important role in the regulation of glomerular hemodynamics and renal expression of cytokines, thus being involved in glomerular hyperfiltration and mesangial expansion in diabetic nephropathy [19-21]. Ang II stimulates TGF-β expression in mesangial cells as well, which may contribute to the development of glomerular sclerosis in diabetes [24-26]. ACE-Is attenuate the development of glomerulosclerosis and tubulointerstitial fibrosis in several animal models and slow disease progression in type 1 diabetic patients [19,74]. Two major renal outcome studies have provided evidence to recommend ARBs as the treatment of choice in type 2 diabetic patients with nephropathy [22,75]. Further, in the Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) study, which was designed to compare the long-term renal outcome of treatment with telmisartan 40 or 80 mg versus enalapril 10 or 20 mg in patients with type 2 diabetes, the change in the glomerular filtration rate after five-year treatment was -17.5 ml per minute per 1.73 m^2 in the telmisartan-treated subjects, as compared with -15.0 ml per minute per 1.73 m^2 in the enalapril-treated subjects [76]. These findings demonstrate that telmisartan is not inferior to enalapril in providing long-term renoprotection in persons with type 2 diabetes, thus supporting the clinical equivalence of ARBs and ACE-Is in persons with conditions that place them at high risk for cardiovascular events. In addition, in UKPDS trial, any reduction in BP was likely to reduce the risk of diabetic vascular complications including nephropathy, with the lowest risk being in those with systolic BP less than 120 mmHg [77]. On the basis of such findings, BP should be controlled as strictly as possible in diabetic patients.

Despite these advances in the therapeutic options for diabetic nephropathy, a numerous number of diabetic patients treated with ACE-Is and ARBs did show only partial anti-proteinuric response, and this heralds a progressive loss of renal function in most cases. Thus, a multidrug approach may be desired. One clinical trials have shown that the combination of the two drugs afford a greater renoprotection than each drug alone. The COOPERATE study compared a combined treatment of ARB and ACE-I, with monotherapy of each drug at its maximum dose, in patients with non-diabetic renal disease [78]. Eleven percent of patients on combination treatment reached the combined primary end point of time to doubling serum creatinine concentration or ESRD compared with 23% of those on ACE-I alone. In diabetic nephropathy, there are small, pilot studies showing that the combined treatment reduced BP and albuminuria more than did single RAS blockade in patients with type 1 or type 2 diabetes [79,80]. Combination therapy with ACE-I and ARBs may be a promising strategy for the treatment of diabetic nephropathy.

Recent experiments have focused on the interaction of the RAS and other pathways thought to be critical to the development of diabetic nephropathy. A number of studies have shown that the RAS and PKC-β are closely interrelated in the kidney as described in the section of PKC [64]. PKC-β can be stimulated by Ang II in the proximal nephrons, and ACE-Is have been shown to reduce diabetes-associated in-

crease in PKC-β activities in glomeruli, in parallel with suppression of albuminuria [81,82]. There are several reports to suggest an intreaction between the RAS and AGEs in diabetic nephropathy as well (Fig. **2**). ACE-I reduces the accumulation of renal and serum AGEs, probably *via* effects on oxidative pathways [83]. Long-term treatment with an ARB may exert salutary effects on AGEs levels in the rat remnant kidney model, probably due to improved renal function [84]. Candesartan, an ARB, reduces AGE accumulation and subsequent albuminuria by down-regulating the NADPH oxidase p47phox component and inducible nitric oxide synthase (iNOS) expression and by attenuating RAGE expression in type 2 diabetic KK/Ta mouse kidneys [85]. In human, administration of ramipril has been recently shown to result in a mild decline of fluorescent non-carboxymethllysine-AGEs and malondialdehyde concentrations in non-diabetic nephropathy patients [86]. In type 2 diabetic subjects, a low-dose of valsartan treatment also decreases serum AGE levels in a BP-independent manner [87]. In addition, we have very recently found that AGE-RAGE-mediated ROS generation activates TGF-β-Smad signaling and subsequently induces mesangial cell hypertrophy and fibronectin synthesis by autocrine production of Ang II [33]. AGEs induce mitogenesis and collagen production in renal interstitial fibroblasts as well *via* Ang II-CTGF pathway [88]. Further, olmesartan medoxomil, an ARB, protects against glomerulosclerosis and renal tubular injury in AGE-injected rats, thus further supporting the concept that AGEs could induce renal damage in diabetes *via* the activation of RAS [89]. Our recent study shows that endothelial cell RAGE expression may be suppressed by telmisartan in patients with essential hypertension [90]. Taken together, these findings may provide an important mechanistic link between metabolic and haemodynamic factors, including the AGE-RAGE system and the RAS, in promoting the development and progression of diabetic nephropathy.

(4) Growth Factors

CTGF has been considered to act as a downstream factor of TGF-β in the development of diabetic nephropathy [91]. Experimental evidence has suggested an active role of CTGF in early- and late-stage morphologic changes of diabetic nephropathy including the damage resulting from hyperglycemia and hypertension, leading to proteinuria and fibrosis. Indeed, increased CTGF expression has been reported in the plasma of type 1 diabetic patients with nephropathy, as well as in glomeruli from diabetic rodents [92]. Recent preliminary study has shown that FG-3019, a recombinant fully human monoclonal antibody designed to bind and neutralize CTGF, normalized kidney filtration and weight in *db/db* mice [93]. FibroGen Inc. intends to initiate a phase II study of FG-3019 in patients with idiopathic pulmonary fibrosis in 2005, but plans are also in place to consider an approach for diabetic nephropathy.

PDGF is a polypeptide that was originally purified from human platelets as a potent mitogen for fibrosis, osteoblasts, smooth muscle and mesangial cells [94,95]. PDGF has been suggested to play a role in the pathogenesis of various fibroproliferative renal diseases [96-98]. Upregulation of the PDGF pathway has been shown in experimental diabetic nephropathy and in the kidneys from patients with diabetes [99]. Aminoguanidine ameliorates diabetic nephropathy *via* suppression of PDGF expression in the kidneys [100]. *In vitro*, inhibition of PDGF results in a significant reduction in mesangial cell proliferation and subsequently prevents the increased deposition of extracellular matrix in the mesangial areas [101]. Moreover, Tsiani *et al*. have demonstrated that

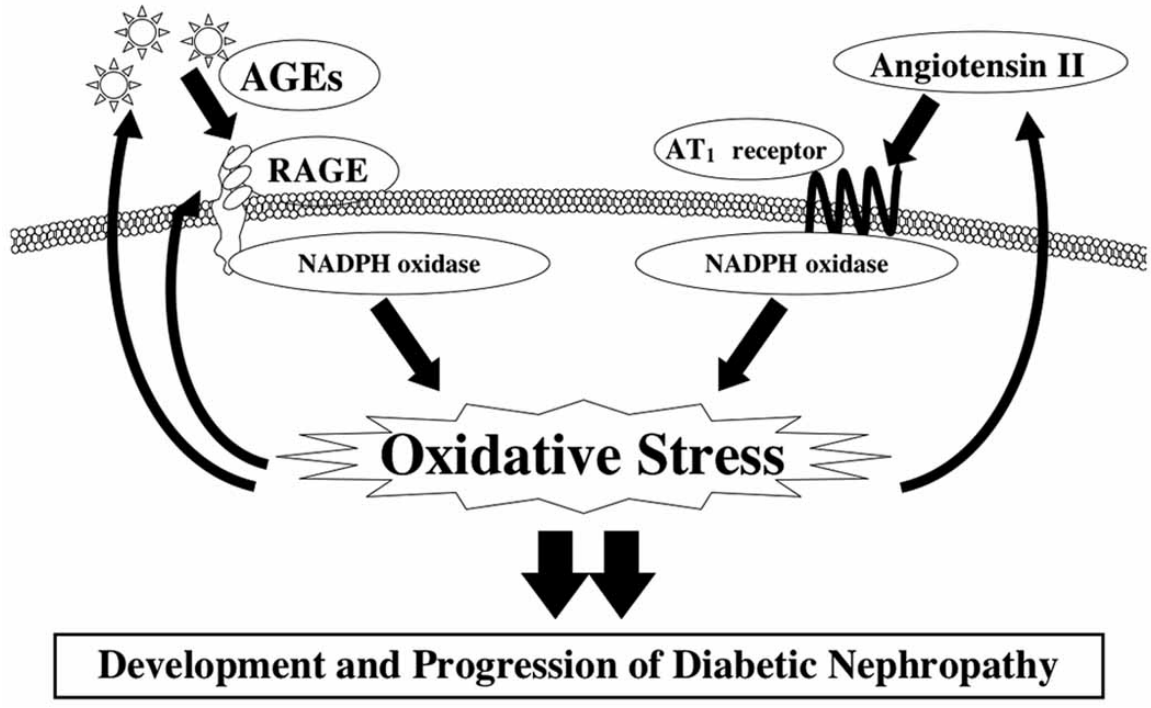

Fig. (2). Crosstalk between the AGE-RAGE system and the RAS in diabetic nephropathy.

high glucose conditions augment the PDGF-induced p38 expression and consequent activation of cAMP responsive element binding (CREB) transcriptional factor in mesangial cells, which might contribute to the pathogenesis of diabetic nephropathy [102]. CuraGen and Abgenix are investigating CR-002, a fully humanized monoclonal antibody that specifically recognizes and blocks the active form of PDGF for the potential treatment of IgA nephropathy. CuraGen and Abgenix are further exploring the utility of this agent as a treatment for other forms of renal diseases, including diabetic nephropathy and nephritis associated with systemic lupus erythematosus.

(5) Peroxisome Proliferator-Activator Receptors (PPARs)

PPARs are members of the nuclear hormone receptor superfamily of ligand-binding transcription factors [103, 104]. Dysregulation of the activity of PPARs has been implicated in obesity, insulin resistance, dyslipidemia, inflammation and hyper-tension [105-107]. Ligands for these receptors include the widely used antidiabetic or insulin-sensitizing thiazolidinediones (TZDs), and more specific synthetic ligands such as derivatives of phenylacetic acid [108]. Clinical use of these agents has improved our understanding of the role of one subtype, PPARγ, in diabetes mellitus [109]. Administration of TZDs to insulin resistant- or type 1 diabetic rats ameliorates albuminuria, glomerular matrix deposition, glomerulosclerosis and tubulointerstitial fibrosis, characteristic changes of diabetic nephropathy [110,111]. *In vitro*, TZDs also prevent high glucose-induced mesangial and tubulointerstitial cell injury [112,113]. In human study, rosiglita-zone is shown to reduce urinary albumin excretion in type 2 diabetes [114]. These renoprotective effects of TZDs are supposed to be due to its anti-inflammatory properties. In addition, Tang *et al.* have recently reported that AGEs stimulate renal tubular expression of adhesion molecule and chemokine that together may account for the transmigration of inflammatory cells into the interstitial space during diabetic tubulopathy. Such proinflammatory phenotype may be partially modified by PPAR-γ ligation through STAT-1 (signal transducer and activator of transcription-1) inhibition independent of NF-κB transcriptional activity and MAPK signaling [115].

CONCLUSION

In this review, we summarize the molecular mechanisms of diabetic nephropathy and provide potential drug targets that prevent this devastating disorder. Unless the specific treatment options that specially target diabetic nephropathy described here has been developed, multifactorial intensified intervention will be a promising therapeutic strategy for treatment of patients with diabetic nephropathy.

ABBREVIATIONS

DCCT = Diabetes Control and Complications Trial

UKPDS = United Kigdom Prospective Diabetes Study

RAS = Renin-angiotensin system

ESRD = End-stage renal disease

AGEs = Advanced glycation end products

ROS = Reactive oxygen species

PKC = Protein kinase C

UARE = Urinary albumin excretion rate

ACE-I = Angiotensin-converting enzyme inhibitor

Ang II = Angiotensin II

ARB = Ang II type 1 receptor blocker

BP = Blood pressure

TGF-β = Transforming growth factor-β

CTGF = Connective tissue growth factor

VEGF = Vascular endothelial growth factor

PDGF-B = Platelet-derived growth factor-B

MAPK = Mitogen activated protein kinase

NF-κB = Nuclear factor-κB

MCP-1 = Monocyte chemoattractant protein-1

RAGE = Receptor for AGEs

DAG = Diacylglycerol

iNOS = Inducible nitric oxide synthase

CREB = cAMP responsive element binding

PPAR = Peroxisome proliferator-activator receptor

TZDs = Thiazolidinediones

STAT-1 = Signal transducer and activator of transcription-1

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