We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Significance of Advanced Glycation End-Products (AGE) and the Receptor for AGE (RAGE) in Diabetic Nephropathy

Tarek Kamal^{1,2}, Yasuhiko Yamamoto^{1,*} and Hiroshi Yamamoto¹

¹Department of Biochemistry and Molecular Vascular Biology
Kanazawa University Graduate School of Medical Science, Kanazawa

²On leave from Kafr EL-Sheikh University

¹Japan

²Egypt

1. Introduction

Diabetic nephropathy is a life-threatening complication of *diabetes mellitus* and the leading cause of end-stage renal disease (ESRD) in developed countries. Diabetes is responsible for over 40% of all new cases with ESRD in the United States and Japan, eventually undergoing renal dialysis or transplantation. Diabetic nephropathy is characterized by glomerular hyperfiltration and thickening of glomerular basement membranes, followed by expansion of extracellular matrix in mesangial area. There are many factors and pathways that are involved in the pathogenesis of diabetic nephropathy. In this chapter, we will focus on advanced glycation end-products (AGE) and the receptor for AGE (RAGE) in the development and prevention of diabetic nephropathy.

2. Possible molecular mechanisms for the development of diabetic nephropathy

Diabetic nephropathy occurs in 20-40% of patients with diabetes and accounts for disabilities and the high mortality rate in patients with diabetes (1). In proportion to the rapid increase of diabetic population, diabetic nephropathy is now the major cause of ESRD in developed countries. There are many factors influencing the development of diabetic nephropathy, this including genetic, hemodynamic, environmental, and metabolic factors. The epidemiological studies have revealed that hyperglycemia *per se* is the most important factor in the onset and progression of diabetic vascular complications (2). Potential mechanisms underlying diabetic nephropathy include activations of polyol and hexosamine pathways, oxidative and nitrosative stress, ER stress, protein kinase C activation, poly(ADP-ribose) polymerase activation, and inflammation (3). Extensive intracellular and extracellular formation of AGE can also become a pathogenic factor in sustained hyperglycemia-induced kidney injuries. Both receptor-dependent and -independent mechanisms are involved in AGE-induced cellular dysfunction and tissue damage.

* Corresponding Author

3. AGE

Reducing sugars like glucose can react nonenzymatically with amino groups of proteins, and a series of further complex molecular rearrangements of dehydration, condensation and crosslinking yield irreversible and heterogeneous derivatives termed AGE (4). AGE are also generated by the reaction of aldehydes and metabolites from glycolysis pathway such as dicarbonyls of methylglyoxal (MG), glyoxal and 3-deoxyglucosone (3DG) with amino acids, lipids and nucleic acids, and through lipid peroxidation (5,6). Although this process takes place continuously within the body during aging, it is extremely accelerated in diabetes (7). There are a large portion of these agents can be exogenous. Tobacco smoke has already been recognized as an important exogenous source of AGE (8). The diet, especially the modern western diet, also provides a relatively large portion of formed AGE and AGE-precursors; e.g. ϵ N-carboxymethyl-lysine (CML) and MG (9). However, the exact nature of various diet-derived AGE derivatives has not yet been fully elucidated.

In vitro, AGE stimulate the generation of reactive oxygen species (ROS), insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), and transforming growth factor- β (TGF- β) in mesangial cells (10, 11), the features characteristic of glomerulosclerosis. AGE also induce TGF- β production in tubular cells, which links to the pathogenesis of tubulointerstitial fibrosis (12). Podocytes undergo apoptosis when exposed to AGE (13), this being implicated in podocyte injuries in diabetes (Fig. 1).

Fig. 1. AGE-RAGE axis and the interaction of other ligands with RAGE contribute to cellular responses and development of diabetic nephropathy. LPS, lipopolysaccharides; PS, phosphatidylserine.

There are three lines of evidence for the role of AGE in diabetic nephropathy. The first line concerns the association between the accumulation of AGE-modified proteins and severity of diabetic nephropathy in both diabetic animals and man (14-17). The second comes from the fact that kidney injuries develop following injection of AGE-modified proteins in non-diabetic animals (18). The third kind of evidence is that the development and progression of diabetic nephropathy is attenuated by the treatment with inhibitors of AGE formation and AGE breakers such as aminoguanidine, pyridoxamine and ALT-711 (19-22).

4. AGE receptors

Accumulating evidence indicates that the interaction of AGE with their receptor can play an important role in the pathogenesis of diabetic nephropathy (23). The best characterized AGE receptor is RAGE. Many other AGE receptors and soluble binding proteins interacting with AGE may also participate in the AGE homeostasis: scavenger receptors class A (MSR-A), class B (MSR-B) (CD36 and LOX1), AGE-R1 (OST48 oligosaccharyltransferase), AGE-R2 (80K-H protein kinase C substrate), AGE-R3 (galectin-3), and toll-like receptor (TLR) 4 (24-28). There are also other molecules like lysozyme and lactoferrin-like polypeptide that play a role in cellular uptake and degradation of AGE (29).

RAGE is a member of the immunoglobulin superfamily, having a total of 394 amino acid residues in the case with human ortholog with a single hydrophobic transmembrane domain (19 amino acids) and a highly charged C-terminal cytosolic tail (43 amino acids) that mediates intracellular signaling pathways (30). Extracellularly, RAGE has an N-terminal immunoglobulin (Ig) V-type ligand binding domain and two Ig C-type domains (V-C-C') (Fig. 2).

Fig. 2. RAGE belongs to an immunoglobulin superfamily and functions as a member of PRRs. LPS, lipopolysaccharides; PS, phosphatidylserine.

AGE-RAGE interaction can induce expressions of genes for vascular endothelial growth factor (VEGF) and for vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells (EC) (31, 32), leading to enhancement of vascular permeability and local inflammation. Secretion of various cytokines such as tumor necrosis factor α (TNF α), interleukin 1 β (IL1 β), IL6, and monocyte chemotactic protein-1 (MCP-1) were induced by the AGE-RAGE system in monocytes and macrophages (33) (Fig. 1). Mammalian homologue of *Drosophila* gene Diaphanous 1 (mDia1) has been identified as a directly binding molecule with an intracellular domain of RAGE and subsequently proven to act as a part of the machinery of RAGE intracellular signaling (34). It is very recently reported that AGE-RAGE interaction can cause phosphorylation of cytoplasmic domain at Ser391 of RAGE by PKC ζ (35) (Fig. 3).

Fig. 3. RAGE intracellular signaling pathways. ERK, extracellular signal-regulated kinase; mDia-1, mammalian Diaphanous-related formin-1; NFκB, nuclear factor κB; PKC ζ , protein kinase C ζ ; JAK-STAT, The Janus kinase-signal transducers and activators of transcription; Ras/MAPK, Ras/mitogen-activated protein kinase; Rac/Cdc42, Rac/Cell division control protein 42 homolog.

RAGE ligands other than AGE have been identified, including high-mobility group box protein 1 (HMGB1), calcium-binding S100 protein group, β 2-integrin Mac/CD11b, amyloid β peptide, β -sheet fibrils, advanced oxidation protein products (AOPP), complement C3a, lipopolysaccharides (LPS), and phosphatidylserine on the surface of apoptotic cells (36-41) (Fig. 2). RAGE is thus considered a member of pattern-recognition receptors like TLRs, actively participating not only in diabetic vascular complications but in the interface of innate and adaptive immunity and in inflammation.

Ligand engagement of RAGE activates the nuclear factor-κB (NF-κB) and other signaling pathways through stimulation of ERK (extracellular signal-regulated kinase)1/2, p38 MAPK

(mitogen-activated protein kinase)-JNK (c-Jun N-terminal kinases), JAK (Janus kinase)-STAT (signal transducer and activator of transcription), and Rac-Cdc42 (42) (Fig. 3). Expression of RAGE is basically low in vascular cells but apparently constitutively induced during diabetes and inflammation. This is explained by the fact that the gene for RAGE *per se* is under the control of NF- κ B, which thus constitutes a positive loop of regulation (43), thereby resulting in the superdrive of the AGE-RAGE system during prolonged hyperglycemic exposure.

5. RAGE and diabetic nephropathy in mice

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 albuminuria. Diabetic nephropathy ultimately proceeds to glomerular sclerosis associated with renal dysfunction.

Because diabetic nephropathy is the major cause of ESRD, the development of effective remedies to retard the progression of diabetic nephropathy has become a pharmaceutical goal. However, it has been hampered by the lack of adequate experimental models to test them (44). We created transgenic (Tg) mice that overexpressed human RAGE in vascular cells by introducing fertilized ovum a transgene carrying human RAGE gene under the control of the murine *flk-1* promoter which works in EC (45). The Tg mice were made

Fig. 4. Periodic acid-Schiff (PAS) stain of the mouse kidneys at 16 weeks of age (ref. 45). Diabetic RAGE-Tg, diabetes-induced RAGE-overexpressing transgenic mice; Diabetic control, diabetes-induced non-transgenic mice; Non-diabetic RAGE-Tg, non-diabetic RAGE-overexpressing transgenic mice; Non-diabetic control, non-diabetic non-transgenic mice.

diabetic by crossbreeding with another Tg line carrying inducible nitric oxide synthase (iNOS) cDNA under the control of insulin promoter (46). The resultant double Tg mice showed significant increases in kidney weight, albuminuria, glomerulosclerosis, and serum creatinine compared with the diabetic iNOS Tg controls (45) (Fig. 4). The sole iNOS Tg mice also showed progression of diabetic nephropathy accompanied by expression of TGF- β in glomeruli (47). Inagi and our group introduced megin (mesangial cell-specific gene with homology to serine protease inhibitor) as the third transgene into RAGE-iNOS double Tg mice, this resulting in further acceleration of the development of nephropathy signs such as mesangial expansion, nodule-like lesion, and tubulointerstitial damage with an increase in local oxidative stress (48). Our group also generated homozygous RAGE knockout (KO) mice and found that the RAGE KO mice displayed suppression of all of the following features of advanced glomerular disease: kidney enlargement, increase in glomerular cell number, mesangial expansion, advanced glomerulosclerosis, albuminuria and the increase in serum creatinine (49). The endothelial-mesenchymal-transition (EndoMT) was also attenuated by the deletion of RAGE (50). That RAGE axis is a crucial cause of diabetic nephropathy has thus clearly emerged from experiments with RAGE-gene manipulated animals. Another model is the OVE26 mouse, in which diabetes is induced by transgene-mediated introduction of calmodulin in pancreatic β -cells (51). RAGE deletion was also beneficial to diabetic nephropathy in the OVE26 diabetic mice (52).

6. Inhibition of AGE and RAGE for the treatment of diabetic nephropathy

A key aim of therapy in diabetic patients is to reduce hyperglycemia by modification of the diet. However, dietary compliance is often difficult, and the alternative is to use pharmacological compounds that can reduce AGE and inhibit RAGE action. There are several endogenous molecular devices that can serve to protect the body from glycation and AGE such as α -ketoglutaraldehyde dehydrogenase, glyoxalase and scavengers (53, 54). Hyperglycemia and RAGE activation are suggested to down-regulate glyoxalase I production and the enzyme activity (55). It is, therefore, rational to take pharmacologic strategies against the down-regulation of those endogenous detoxication enzymes.

Applications of inhibitors for AGE and RAGE may be promising therapeutic approaches for diabetic nephropathy (Table 1). Antioxidants may protect against free radicals derived from autooxidative glycation and AGE. Benfotiamine is a synthetic S-acyl derivative of thiamine and has anti-oxidant and anti-AGE formation (56). Amadoriases may be used to deglycate Amadori products or to inactivate intermediates such as 3DG. AGE-crosslink breakers such as ALT-711 (algebrium) and *N*-phenylthiazolium bromide (PTB) offer the potential of reversing diabetic nephropathy, although their precise mechanism of action is still unclear (57, 58). TTP488 is an antagonist against RAGE, which is under clinical studies, and neutralizing anti-RAGE antibody may also be useful (59). Low-molecular weight heparin (LMWH) can bind RAGE and act as an antagonist to RAGE [31]. LMWH treatment of the mouse model of diabetic nephropathy showed both the preventive and therapeutic effects on albuminuria and glomerulosclerosis in a dose-dependent manner (49). Thiazolidinediones, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), and statins are reported to suppress RAGE expression (60, 61). There are numerous compounds that have been investigated for the anti-glycation activity but their use in humans is still debatable (62). Decoy type receptors of

RAGE, namely soluble RAGE (sRAGE), is also applicable for the treatment of diabetic nephropathy. sRAGE corresponds to the extracellular domain of RAGE lacking the transmembrane and cytosolic domains. As the N-terminal V-type domain is included, sRAGE has the same ligand-binding ability as membrane RAGE and thus is able to act as a decoy by preventing the ligands to reach the membrane-bound counterpart. In *db/db* mice, treatment with murine sRAGE (50 mg/day for 19 weeks) decreased albuminuria, glomerulosclerosis and GBM thickening (63); the sRAGE employed in that study was the truncated form of RAGE artificially produced by recombinant gene technology. Endogenous sRAGE exists in the circulation of humans. To generate sRAGE endogenously, two mechanisms are considered: (1) the alternative splicing to remove the transmembrane region and (2) the proteolytic cleavage from the cell surface. We identified and reported a splice variant form of soluble RAGE and named it endogenous secretory RAGE (esRAGE) (64, 65). Reinforcing sRAGE genesis by ectodomain shedding will decrease an amount of signal-transducing RAGE and will in turn reciprocally increase an amount of decoy receptor sRAGE; this can control ligand-RAGE signaling and subsequent cellular derangement in the kidney. Treatment with statins and ACEI is reported to stimulate circulating sRAGE production in human studies (66, 67). Further investigations are needed for better understanding of the regulation of sRAGE production and for developing drugs that can simultaneously upregulate sRAGE and downregulate mRAGE.

AGE inhibitors	Pyridoxamine
	Benfotiamine
AGE-crosslink brakers	GLY-230
	PTB
	ALT-711 (Algebrium)
	C36
RAGE inhibitors	TRC4186
	LMWH
	TTP488/PF04494700
	TTP3000, TTP4000
sRAGE	ACEI
	ARB
	TZD

PTB, N-phenacylthiazolium bromide; LMWH, low-molecular weight heparin; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; TZD, thiazolidinedione; sRAGE, soluble RAGE.

Table 1. Inhibitors of AGE and RAGE

7. Conclusions

Accumulating evidence has supported the concept that AGE and RAGE play an active role in the development and progression of diabetic nephropathy. Prophylactic and therapeutic strategies focusing on RAGE and its ligand axis will be of great importance in conquering diabetic kidney injuries.

8. References

- [1] Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. *Diabetes Care* 2005; 28:164-176.
- [2] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977-986.
- [3] Pacher P, Szabó C. Role of poly(ADP-ribose) polymerase-1 activation in the pathogenesis of diabetic complications: endothelial dysfunction, as a common underlying theme. *Antioxid Redox Signal* 2005; 7(11-12): 1568-1580.
- [4] Brownlee M, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. *N Eng J Med* 1988; 318(20): 1315-1321.
- [5] Nagai R, Mori T, Yamamoto Y, Kaji Y, Yonei Y. Significance of advanced glycation endproducts (AGEs) in aging-related disease. *Anti-Aging Med* 2010; 7(10): 112-119.
- [6] Fu MX, Requena JR, Jenkins AJ, Lyons TJ, Baynes JW, Thorpe SR. The advanced glycation end products, Nepsilon-(carboxymethyl)lysine, is a product of both lipid peroxidation and glycoxidation reactions. *J Biol Chem* 1996; 271:9982-9986.
- [7] Thorpe SR, Baynes JW. Role of the Millard reaction in diabetes mellitus and diseases of aging. *Drugs Aging* 1996; 9: 69-77.
- [8] Cerami C, Founds H, Nicholl I, Mitsuhashi T, Giordano D, Vanpatten S, Lee A, Al-Abed Y, Vlassara H, Bucala R, Cerami A. Tobacco smoke is a source of toxic reactive glycation products. *Proc Natl Acad Sci USA* 1997; 94(25): 13915-13920.
- [9] Vlassara H, Palace MR. Diabetes and advanced glycation endproducts. *J Intern Med* 2002; 251: 87-101.
- [10] Yamagishi S, Inagaki Y, Okamoto T, et al. Advanced glycation end products inhibit de novo protein synthesis and induce TGF-beta overexpression in proximal tubular cells. *Kidney Int* 2003; 63: 464-473.
- [11] Doi T, Vlassara H, Kirstein M, Yamada Y, Striker GE, Striker LJ. Receptor-specific increase in extracellular matrix production in mouse mesangial cells by advanced glycosylation end products is mediated via platelet-derived growth factor. *Proc Natl Acad Sci USA* 1992; 89(7): 2873-2877.
- [12] Sharma K, Ziyadeh FN. Hyperglycemia and diabetic kidney disease. The case for transforming growth factor-beta as a key mediator. *Diabetes* 1995; 44: 1139-1146.
- [13] Chuang PY, Yu Q, Fang W, Uribarri J, He JC. Advanced glycation endproducts induce podocyte apoptosis by activation of the FOXO4 transcription factor. *Kidney Int* 2007; 72(8): 965-976.
- [14] Sugiyama S, Miyata T, Horie K, Lida Y, Tsuyuki M, Tanaka H, et al. Advanced glycation endproducts in diabetic nephropathy. *Nephrol Dial Transplant* 1996; 11: 91-94.
- [15] Sell DR, Lapolla A, Odetti P, Fogarty J, Monnier VM. Pentosidine formation in skin correlates with severity of complications in individuals with long-standing IDDM. *Diabetes* 1992; 41: 1286-1292.
- [16] McCance DR, Dyer DG, Dunn JA, Bailie KE, Thorpe SR, Baynes JW, Lyons TJ. Millard reaction products and their relation to complications in insulin-dependent diabetes mellitus. *J Clin Invest* 1993; 91: 2470-2478.
- [17] Beisswenger PJ, Makita Z, Curphey TJ, Moore LL, Jean S, Brinck-Johnsen T, Bucala R, Vlassara H. Formation of immunochemical advanced glycation endproducts

- precedes and correlates with early manifestations of renal and retinal disease in diabetes. *Diabetes* 1995; 44: 824-829.
- [18] Vlassara H, Striker LJ, Teichberg S, Fuh H, Li YM, Steffes M. Advanced glycation endproducts induce glomerular Sclerosis and albuminuria in normal rats. *Proc Natl Acad Sci USA* 1994; 91: 11704-11708.
- [19] Hammes HP, Strodter D, Weiss A, Bretzel RG, Federlin K, Brownlee M. Secondary intervention with aminoguanidine retards the progression of diabetic nephropathy in the rat model. *Diabetologia* 1995; 38: 656-660.
- [20] Soulis T, Cooper ME, Satra S, Thallas V, Panagiotopoulos S, Bjerrum OJ, Jerums G. Relative contributions of advanced glycation and nitric oxide synthase inhibition to aminoguanidine-mediated renoprotection in diabetic rats. *Diabetologia* 1997; 40: 1141-1151.
- [21] Degenhardt TP, Alderson NL, Arrington DD, Beattie RJ, Basgen JM, Steffes MW, Thorpe SR, Baynes JW. Pyridoxamine inhibits early renal disease and dyslipidemia in the streptozotocin-diabetic rat. *Kidneys Int* 2002; 61: 939-950.
- [22] Thallas-Bonke V, Lindschau C, Rizkalla B, Bach LA, Boner G, Meier M, Haller H, Cooper ME, Forbes JM. Attenuation of extracellular matrix accumulation in diabetic nephropathy by the advanced glycation end product cross-link breaker ALT-711 via a protein kinase C-alpha-dependent pathway. *Diabetes* 2004; 53(11): 2921-2930.
- [23] Yamamoto H, Watanabe T, Yamamoto Y, *et al.* RAGE in diabetic nephropathy. *Curr Mol Med* 2007; 7 (8): 752-757.
- [24] Yang Z, Makita Z, Horii Y, *et al.* Two novel rat liver membrane proteins that bind advanced glycosylation endproducts: relationship to macrophage receptor for glucose-modified proteins. *J Exp Med* 1991; 174(3): 515-524.
- [25] Vlassara H, Li YM, Imani Y, *et al.* Identification of galectin-3 as a high-affinity binding protein for advanced glycation end products (AGE): a new member of the AGE-receptor complex. *Mol Med* 1995; 1(6): 634-646.
- [26] Zhu W, Sano H, Nagai R, Fukuhara K, Miyazaki A, Horiuchi S. The role of galectin-3 in endocytosis of advanced glycation end products and modified low density lipoproteins. *Biochem Biophys Res Commun* 2001; 280(4): 1183-1188.
- [27] Suzuki H, Kurihara Y, Takeya M, *et al.* A role for macrophage scavenger receptors in atherosclerosis and susceptibility to infection. *Nature* 1997; 386(6633): 292-296.
- [28] Hodgkinson CP, Laxton RC, Patel K, Ye S. Advanced glycation end-product of low density lipoprotein activates the toll-like 4 receptor pathway implications for diabetic atherosclerosis. *Arterioscler Thromb Vasc Biol* 2008; 28(12): 2275-2281.
- [29] Mitsuhashi T, Li YM, Fishbane S, Vlassara H. Depletion of reactive advanced glycation endproducts from diabetic uremic sera using a lysozyme-linked matrix. *J Clin Invest* 1997; 100(4): 847-854.
- [30] Bierhaus A, Humpert PM, Morcos M, *et al.* Understanding RAGE, the receptor for advanced glycation endproducts. *J Mol Med* 2005; 83: 876-886.
- [31] Yamagishi S, Yonekura H, Yamamoto Y, *et al.* Advanced glycation end products-driven angiogenesis in vitro. Induction of the growth and tube formation of human microvascular endothelial cells through autocrine vascular endothelial growth factor. *J Biol Chem* 1997; 272(13):8723-8730.

- [32] Yamamoto Y, Yonekura H, Watanabe T, *et al.* Short-chain aldehyde-derived ligands for RAGE and their actions on endothelial cells. *Diabetes Res Clin Pract* 2007; 77 (S1): 30-40.
- [33] Hou FF, Miyata T, Boyce J, *et al.* beta(2)-Microglobulin modified with advanced glycation end products delays monocyte apoptosis. *Kidney Int* 2001; 59(3): 990-1002.
- [34] Hudson BI, Kalea AZ, Arriero MDM, *et al.* Interaction of the RAGE cytoplasmic domain with diaphanous-1 is required for ligand-stimulated cellular migration through activation of Rac1 and Cdc42. *J Biol Chem* 2008; 283(49): 34457-34468.
- [35] Sakaguchi M, Murata H, Yamamoto K, *et al.* TIRAP, an adaptor protein for TLR2/4, transduces a signal from RAGE phosphorylated upon ligand binding. *PLoS One* 2011; 6(8): e23132.
- [36] Hori O, Brett J, Slattery T, *et al.* The receptor for advanced glycation end products (RAGE) is a cellular binding site for amphoterin. Mediation of neurite outgrowth and co-expression of rage and amphoterin in the developing nervous system. *J Biol Chem* 1995; 270(43): 25752-25761.
- [37] Hofmann MA, Drury S, Fu C, *et al.* RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. *Cell* 1999; 97(7): 889-901.
- [38] Yan SD, Chen X, Fu J, *et al.* RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. *Nature* 1996; 382(6593): 685-691.
- [39] Chavakis T, Bierhaus A, Al-Fakhri N, *et al.* The pattern recognition receptor (RAGE) is a counter receptor for leukocyte integrins: a novel pathway for inflammatory cell recruitment. *J Exp Med* 2003; 198(10): 1507-1515.
- [40] Yamamoto Y, Harashima A, Saito H, *et al.* Septic shock is associated with receptor for advanced glycation end products ligation of LPS. *J Immunol* 2011; 186(5): 3248-3257.
- [41] He M, Kubo H, Morimoto K, *et al.* Receptor for advanced glycation end products binds to phosphatidylserine and assists in the clearance of apoptotic cells. *EMBO Rep* 2011; 12(4): 358-364.
- [42] Barlovic DP, Soro-Paavonen A, Jandeleit-Dahm KA. RAGE biology, atherosclerosis and diabetes. *Clin Sci (Lond)* 2011; 121(2): 43-55.
- [43] Tanaka N, Yonekura H, Yamagishi S, *et al.* The receptor for advanced glycation end products is induced by the glycation products themselves and tumor necrosis factor-alpha through nuclear factor-kappa B, and by 17beta-estradiol through Sp-1 in human vascular endothelial cells. *J Biol Chem* 2000; 275(33): 25781-25790.
- [44] Inagi R, Nanagaku M, Miyata T. Synergistic contribution of carbonyl stress and megsin in diabetic nephropathy. *Ann NY Acad Sci* 2005; 1043: 605-608.
- [45] Yamamoto Y, Kato I, Doi T, *et al.* Development and prevention of advanced diabetic nephropathy in RAGE-overexpressing mice. *J Clin Invest* 2001; 108(2): 261-268.
- [46] Takamura T, Kato I, Kimura N, *et al.* Transgenic mice overexpressing type 2 nitric-oxide synthase in pancreatic beta cells develop insulin-dependent diabetes without insulinitis. *J Biol Chem* 1998; 273(5): 2493-2496.
- [47] Ohashi S, Abe H, Takahashi T, Yamamoto Y, Takeuchi M, Arai H, Nagata K, Kita T, Okamoto H, Yamamoto H, Doi T. Advanced glycation end products increase collagen-specific chaperone protein in mouse diabetic nephropathy. *J Biol Chem* 2004; 279: 19816-19823.

- [48] Inagi R, Yamamoto Y, Nangaku M, *et al.* A severe diabetic nephropathy model with early development of nodule-like lesions induced by megsin overexpression in RAGE/iNOS transgenic mice. *Diabetes* 2006; 55(2): 356-366.
- [49] Myint KM, Yamamoto Y, Doi T, *et al.* RAGE control of diabetic nephropathy in a mouse model: effects of RAGE gene disruption and administration of low-molecular weight heparin. *Diabetes* 2006; 55(9):2510-2522.
- [50] Li L, Qu X, Yao J, *et al.* Blockade of endothelial-mesenchymal transition by a Smad 3 inhibitor delays the early development of streptozotocin-induced diabetic nephropathy. *Diabetes* 2010; 59(10): 2612-2624.
- [51] Zheng S, Noonan WT, Metreveli NS, Coventry S, Kralik PM, Carlson EC, Epstein PN. Development of late-stage diabetic nephropathy in OVE26 diabetic mice. *Diabetes* 2004; 53(12): 3248-3257.
- [52] Reinger N, Lau K, McCalla D, *et al.* Deletion of the receptor for advanced glycation end products reduces glomerulosclerosis and preserves renal function in the diabetic OVE26 mouse. *Diabetes* 2010; 59(8): 2043-2054.
- [53] Hata F, Igaki N, Nakamichi T, Masuda S, Nishimoto S, Oimomi M, *et al.* Suppressive effect of α -Ketoglutaraldehyde dehydrogenase on the advanced process of the Millard reaction. *Diabetes Res Clin Practice* 1988; 5: 5413.
- [54] Thornalley PJ. The glyoxalase system: new developments towards functional characterization of a metabolic pathway fundamental to biological life. *Biochem J* 1990; 269(1): 1-11.
- [55] Xue M, Rabbani N, Thornalley PJ. Glyoxalase in ageing. *Semin Cell Dev Biol* 2011; 22(3): 293-301.
- [56] Stirban A, Negrean M, Stratmann B, *et al.* Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. *Diabetes Care* 2006; 29(9): 2064-2071.
- [57] Schwedler SB, Verbeke P, Bakala H, *et al.* N-phenacylthiazolium bromide decreases renal and increases urinary advanced glycation end products excretion without ameliorating diabetic nephropathy in C57BL/6 mice. *Diabetes Obes Metab* 2001; 3(4): 230-239.
- [58] Wolffenbuttel BH, Bouanger CM, Crijns FR, *et al.* Breakers of advanced glycation endproducts restore large artery properties in experimental diabetes. *Proc Natl Acad Sci USA* 1998; 95(8): 4630-4634.
- [59] Jensen IJ, Denner I, Schrijers BF, Tilton RG, Rash R, Flyvbjerg A. Renal effects of a neutralizing RAGE-antibody in long term streptozotocin-diabetic mice. *J Endocrinol* 2006; 188: 493-501.
- [60] Marx N, Walcher D, Ivanova N, *et al.* Thiazolidinediones reduce endothelial expression of receptors for advanced glycation end products. *Diabetes* 2004; 53(10): 2662-2668.
- [61] Yamagishi S, Takeuchi M. Nifedipine inhibits gene expression of receptor for advanced glycation end products (RAGE) in endothelial cells by suppressing reactive oxygen species generation. *Drugs Exp Clin Res* 2004; 30(4): 169-175.
- [62] Ahmed N. Advanced glycation endproducts-role in pathology of diabetic complications. *Diabetes Res Clin Pract* 2005; 67: 3-21.

- [63] Wendt T, Tanji N, Guo J, Kislinger TR, Qu W, Lu Y, et al. RAGE drives the development of glomerulosclerosis and implicates podocyte activation in the pathogenesis of diabetic nephropathy. *Am J Pathol* 2003; 162: 1123-1137.
- [64] Yonekura H, Yamamoto Y, Sakurai S, et al. Novel splice variants of the receptor for advanced glycation end-products expressed in human vascular endothelial cells and pericytes, and their putative roles in diabetes-induced vascular injury. *Biochem J* 2003; 370(3): 1097-1109.
- [65] Harashima A, Yamamoto Y, Cheng C, et al. Identification of mouse orthologue of endogenous secretory receptor for advanced glycation end-products: structure, function and expression. *Biochem J* 2006; 396(1): 109-115.
- [66] Cuccurullo C, Lezzi A, Fazia ML, et al. Suppression of RAGE as a basis of simvastatin-dependent plaque stabilization in type 2 diabetes. *Arterioscler Thromb Vasc Biol* 2006; 26(12): 2716-2723.
- [67] Santilli F, Bucciarelli L, Noto D, et al. Decreased plasma soluble RAGE in patients with hypercholesterolemia: effects of statins. *Free Radic Biol Med* 2007; 43(9): 1255-1262.

IntechOpen

Diabetic Nephropathy

Edited by Dr. John Chan

ISBN 978-953-51-0543-5

Hard cover, 166 pages

Publisher InTech

Published online 20, April, 2012

Published in print edition April, 2012

Internationally renowned experts have provided data on their own studies, and discuss the relative usefulness of their work in relation to diabetic nephropathy. The first section describes the novel role of intrarenal renin-angiotensin-aldosterone system (RAAS) and oxidative stress in the development of diabetic nephropathy and discusses the current and novel pharmacological interventions in the treatment of diabetic nephropathy. The second section discusses other important contributors outside of the RAAS in the pathogenesis of diabetic nephropathy including AGE/RAGE, epithelial-mesenchymal-transition (EMT) and immune cytokines. Features: Provides novel information on various pathophysiological determinants in the development of diabetic nephropathy Provides novel information on various pharmacological interventions of diabetic nephropathy

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Tarek Kamal, Yasuhiko Yamamoto and Hiroshi Yamamoto (2012). Significance of Advanced Glycation End-Products (AGE) and the Receptor for AGE (RAGE) in Diabetic Nephropathy, Diabetic Nephropathy, Dr. John Chan (Ed.), ISBN: 978-953-51-0543-5, InTech, Available from: <http://www.intechopen.com/books/diabetic-nephropathy/pathogenesis-of-diabetic-nephropathy-significance-of-advanced-glycation-end-products-age-and-the-rec>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen