Advanced glycation end products and the kidney

Jürgen M. Bohlender, Sybille Franke, Günter Stein, and Gunter Wolf

Department of Internal Medicine III, Friedrich-Schiller-University, Jena, Germany

Invited Review

Bohlender, Jürgen M., Sybille Franke, Günter Stein, and Gunter Wolf. Advanced glycation end products and the kidney. Am J Physiol Renal Physiol 289: F645–F659, 2005; doi:10.1152/ajprenal.00398.2004.—Advanced glycation end products (AGEs) are a heterogeneous group of protein and lipids to which sugar residues are covalently bound. AGE formation is increased in situations with hyperglycemia (e.g., diabetes mellitus) and is also stimulated by oxidative stress, for example in uremia. It appears that activation of the renin-angiotensin system may contribute to AGE formation through various mechanisms. Although AGEs could nonspecifically bind to basement membranes and modify their properties, they also induce specific cellular responses including the release of profibrogenic and proinflammatory cytokines by interacting with the receptor for AGE (RAGE). However, additional receptors could bind AGEs, adding to the complexity of this system. The kidney is both: culprit and target of AGEs. A decrease in renal function increases circulating AGE concentrations by reduced clearance as well as increased formation. On the other hand, AGEs are involved in the structural changes of progressive nephropathies such as glomerulosclerosis, interstitial fibrosis, and tubular atrophy. These effects are most prominent in diabetic nephropathy, but they also contribute to renal pathophysiology in other nondiabetic renal diseases. Interference with AGE formation has therapeutic potential for preventing the progression of chronic renal diseases, as shown from data of animal experiments and, more recently, the first clinical trials.

RAGE: diabetic nephropathy; progression of renal disease; inflammation; glycoxidation

Address for reprint requests and other correspondence: G. Wolf, Klinik für Innere Medizin III, Universitätsklinik Jena, Erlanger Allee 101, Jena, Germany (e-mail: Gunter.Wolf@med.uni-jena.de).

REDUCING SUGARS MAY REACT nonenzymatically with amino groups in proteins or lipids, involving a series of complex biochemical events with oxidative and nonoxidative molecular rearrangements termed the Maillard reaction that ultimately lead to stable covalent adducts known as advanced glycation end products (AGEs). The reaction proceeds slowly through different stages, leading to alterations of protein structure and molecular surface topology that profoundly change the affected molecule’s biochemical properties. Using antibodies raised against AGE-specific epitopes, AGEs have been detected in human tissues under physiological conditions where their concentrations increase with chronological age, thereby linking AGEs to long-term protein degeneration and biological aging (36). Virtually any protein can become a target of glycoxidative modifications in vivo. Long-lived proteins, however, including matrix and structural proteins in tissue compartments with slow biological turnover, such as the lens or extracellular matrix (ECM), are particularly prone to AGE modification under conditions that favor their generation. AGE accumulation in tissues may result from accelerated AGE generation, decreased AGE degradation, or increased survival of AGEs. Increased tissue or plasma AGE concentrations have been detected in a variety of common diseases, including diabetes mellitus, chronic renal failure, atherosclerosis, arterial hypertension, and Alzheimer’s disease, whereas their pathophysiological implications are only recently becoming understood in more detail. Furthermore, AGEs are found also in primary rheumatoid arthritis and during osteoporosis. These findings underscore the universal pathogenetic role of AGEs (48, 138). Following the recent detection of specific receptors that recognize AGE-modified proteins (RAGE), activate intracellular signaling cascades, and finally orchestrate a plethora of proinflammatory and profibrotic cellular responses, current research has centered on the pathophysiological implications of AGE-RAGE interactions in a rapidly growing field of biomedical research (119).

AGEs and their receptors have now been established as a major pathogenic factor promoting complications of diabetes mellitus. In addition, they are also intrinsically involved in the pathophysiology of many other nondiabetic renal diseases. The pivotal role of AGEs during glomerular and tubulointerstitial damage and the development of uremic complications is now increasingly recognized as is their role in amplifying local immune and inflammatory responses in the kidney. In this context, the kidney is not only a target of AGEs but also a culprit because declining renal function entails a rapid increase in plasma concentrations of these products, thereby setting the stage for a vicious circle with deleterious consequences for the organ’s survival. A complete review of the burgeoning literature dealing with AGEs and AGE-specific diseases is beyond the scope of this contribution. The interested reader is referred to several excellent reviews on these topics (7, 85, 120, 128, 151, 152). Here, we will focus on research related to increased AGE generation in uremic conditions and to the AGE-RAGE interaction in the kidney under physiological and pathological conditions.
FORMATION OF AGEs AND “CARBONYL STRESS”

The basic biochemical steps leading to the generation of AGEs are shown in Fig. 1. The initial reaction between reducing sugars and a protein proceeds through the formation of a labile Schiff’s base, a rapid and easily reversible reaction that may halt at this point. The reaction product, however, may eventually continue to isomerize while slowly forming a ketoamine adduct termed the Amadori product. A typical Amadori compound, for instance, is hemoglobin A1c being used as a classic long-term marker for glycemia in diabetes mellitus. Such early products can undergo further complex oxidative decomposition, condensation, and additional molecular rearrangements that ultimately lead to stable, irreversible late AGEs, a process that may take weeks or months to accomplish. To fuel this process, glucose is an ubiquitous and predominant substrate, but other sugar molecules such as fructose, threose, glucose 6-phosphate, and glyceraldehyde 3 phosphate may also react similarly with proteins and produce chemically distinct AGEs according to the reaction partners, respectively (87, 128). Some important AGE compounds are listed in Table 1.

In diabetes, hyperglycemia leads to the activation of alternative intracellular metabolic pathways (e.g., polyol pathway) that foster the generation of these sugar moieties. Nε-carboxymethyllysine (CML), Nε-carboxyethyllysine (CEL), and pentosidine are major representatives of this class of AGEs. Furthermore, pentosidine is a cross-linking molecule that covalently bridges distant lysine and arginine residues in proteins by a complex C5-ring, thereby linking different proteins together or forming intramolecular covalent bonds. Alternatively, these adducts can arise from intermediate lipid metabolism, for instance, by oxidation of polyunsaturated fatty acids and arachidonic acid involving metal ion-catalyzed reactions. Protein adducts arising from this pathway are accordingly termed advanced lipoperoxidation end products (ALEs). Compounds such as malondialdehyde (MDA)-lysine, hydroxynonenal (HNE)-lysine, or acrolein adducts derived from oxidized hydroxy-amino acids, l-serine or l-threonine, belong to this class of terminally modified proteins. The term AGE is frequently used for both groups of compounds, and for reasons of simplicity this practice will be maintained here. Glycoxidative and lipoxidative pathways may independently result in the same end product CML, whereas pentosidine, for instance, is only formed from carbohydrate precursors. In contrast, AGEs such as imidazolone and pyrraline can also be generated independently from oxidative stress. Nonoxidative chemistry, finally, is involved in the generation of AGEs from methylglyoxal, for instance, during nonoxidative anaerobic glycolysis or based on 3-deoxyglucosone released during Amadori rearrangements (84, 85, 87, 101). Interestingly, these reactions are strongly influenced by the individual genetic background, although the genes responsible for this feature still remain unknown. Leslie and collaborators (66) performed a classic study in 39 monozygotic and 45 dizygotic otherwise healthy nondiabetic female twins. They showed that correlations for serum CML levels were higher in monozygotic (r = 0.71)

### Table 1. Biologically important AGEs (3)

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Non-cross-linking monolysyl adducts</td>
<td>Nε-carboxymethyllysine (CML)</td>
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<tr>
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<td>Nε-carboxyethyllysine (CEL)</td>
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<td>Pyrraline</td>
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<td>Cross-linking bislysyl adducts</td>
<td>Glyoxal-derived lysine dimer (GOLD)</td>
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<td>Methylglyoxal-derived lysine dimer (MOLD)</td>
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<td>3-Deoxyglucosone-derived lysine dimer (DOLD)</td>
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<tr>
<td>Hydroimidazolones</td>
<td>Glyoxal-derived hydroimidazolone (G-H)</td>
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<td>Methylglyoxal hydroimidazolone (MG-H)</td>
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<td></td>
<td>3-Deoxyglucosone-derived lysine dimer (3DG-H)</td>
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<tr>
<td>Other cross-linking compounds</td>
<td>Pentosidine*</td>
</tr>
</tbody>
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AGEs, advanced glycation end products. *Forms intermolecular links between arginine and lysine residues.
compared with dizygotic twins ($r = 0.50$). The overall heritability was calculated at 74%, independent of genes influencing fasting glucose and hemoglobin A1c levels.

Diabetes mellitus and uremia are both conditions where significantly increased concentrations of AGEs are found in tissues and in plasma (72). Plasma pentosidine concentrations, for instance, may be up to 10-fold higher in patients with end-stage renal disease compared with normal subjects (81, 135). In diabetic patients, elevated glucose levels could readily explain their propensity to form AGEs, for instance, by shifting the biochemical reaction equilibrium toward glycation (Schiff’s reaction) in a concentration-dependent manner, followed by irreversible AGE formation. Diabetics, however, are also characterized by chronic hyperlipidemia. Recently, Metz et al. (77) were able to demonstrate that diabetic animals treated with pyridoxamine to inhibit AGE formation produced considerable amounts of ALEs derived form polyunsaturated fatty acids. Treated animals furthermore excreted increased amounts of pyridoxamine-linked intermediates derived from fatty acids and arachidonate in their urine, indicating a pharmacological trapping mechanism. In their study, they provided experimental evidence that ALE formation is an important alternative pathway that quantitatively contributes to the accumulation of carbonyl-modified proteins in diabetes.

In uremic patients, AGE levels in plasma and tissues increase independently of glycemia because diabetic and nondiabetic patients on chronic maintenance hemodialysis show similar total concentrations of serum AGEs such as pentosidine, CML, and ALEs. Additionally, AGE levels in uremic patients on hemodialysis were found to be several times higher than in patients with diabetes and a normal kidney function. Mechanisms other than hyperglycemia therefore must be involved additionally (81, 84). In uremic plasma, accumulation of low-molecular-weight reactive carbonyl compounds such as 3-deoxyglucosone, dehydroascorbate, glyoxal, methylglyoxal, malondialdehyde, and arabinose derived from carbohydrate, lipid, or amino acid metabolism has been noted as a general feature. The presence in uremia of these reactive AGE precursors, termed reactive carbonyl compounds (RCO), together with carbonyl-modified proteins (AGEs), has therefore been summarized as a state of uremic carbonyl stress and pinpointed as a major pathogenic mechanism and risk factor for uremic end-organ damage (85, 87). Plasma pentosidine concentrations, for instance, have been shown to correlate directly with the amount of generated carbonyl precursors and may serve as a simple integral marker of uremic carbonyl stress. Uremic plasma, on long-term in vitro incubation, shows increased formation of pentosidine compared with nonuremic plasma, documenting its higher autoreactive potential. Addition of OPB-9195, an inhibitor of protein-RCO interaction, to uremic plasma samples inhibited pentosidine formation, supporting this pathogenic concept (82). One primary origin of increased carbonyl stress is oxidative stress, as observed by an increased amount of oxidized compounds and markers of oxidative stress in uremic plasma such as oxidized ascorbate (dehydroascorbate) or oxidized glutathione, which may subsequently contribute to increased RCO formation (85, 89). The relevance of this mechanism is underscored by the observation that AGEs are generated also in nonuremic normoglycemic animal models at sites of increased local oxidant stress or in situations with decreased antioxidant capacity, for instance, during the development of arteriosclerotic lesions or plaque. Local generation of peroxynitrite from nitric oxide (NO) may contribute to this effect (95). Furthermore, accumulation of AGEs can be found at sites with endothelial injury with inflammatory neointimal proliferation but also during chronic arterial wall remodeling in arterial hypertension or during development of diabetic glomerular disease (91, 138, 171). Finally, myeloperoxidase-dependent generation of reactive oxygen species (ROS) by mononuclear cells at sites of inflammation may stimulate local AGE formation as an active cell-dependent process. For instance, macrophages releasing ROS into the intercellular space may foster extracellular AGE generation in their vicinity (6). Intracellular accumulation of AGEs increased directly with generation of ROS in endothelial cells (45). During chronic renal failure, there is a decreased ability of the body to clear reactive carbonyl compounds from the circulation, which contributes to globally increased RCO stress in this situation. The defective physiological RCO clearance in uremia is a consequence of a decreased availability of detoxifying scavenger molecules or RCO-degrading enzymes, together with a reduced clearance of RCO into the urine by the failing kidney itself. The lack of glutathione and its replenishing redox coenzyme NADPH as well as the markedly reduced concentrations of many other glutathione-dependent enzymes are a characteristic of uremia and are inversely related to high plasma pentosidine concentrations, the integral RCO marker (145). In patients with progressive renal failure, plasma pentosidine concentrations have been shown to increase in parallel with declining kidney function, supporting this pathophysiological concept (72, 135).

Using size-exclusion chromatography and fluorescence techniques, three main AGE fractions in uremic plasma have been found at a predominant molecular size of $\sim 70$, $\sim 14$, and $<2$ kDa, respectively (51). Pentosidine and CML are the prevalent AGE species, and most of their concentration is bound to serum albumin ($\sim 90\%$) displaying a molecular weight of $\sim 69$ kDa (81, 84). These high-molecular-weight AGEs, therefore, cannot be cleared by hemodialysis or glomerular filtration in significant amounts while the effect of different dialysis modalities on total plasma AGE concentrations is generally limited (132). Hemodialysis instead allows quantitative elimination of their much smaller reactive carbonyl precursors, with a typical molecular weight $<5,000$ Da (82, 102). The remaining serum AGE fraction represents free pentosidine and AGE-bound to small peptides of low molecular weight, which may appear in the urine depending on their seize. After being filtered into the urine, small AGE molecules may undergo further degradation and modification while being reabsorbed partly by proximal tubular cells (9, 80). Low-molecular-weight AGE peptides, however, may possibly have a higher toxic potential for tubular cells than the larger AGE proteins (34). Interestingly, after kidney transplantation the long-lived high-molecular-weight AGE fraction does not disappear rapidly from the circulation despite marked improvement of renal function. The quantitatively very small low-molecular-weight AGE fraction, however, decreases immediately, which has been attributed to improved renal AGE excretion and increased renal metabolism (41, 83). Three years after transplantation, specific AGE compounds, however, may decrease to serum levels found in chronic renal failure. Furthermore, in a recent study there was no apparent association of...
serum AGE levels found in chronic renal failure with cardiovascular risk (131). Taken together, the reduced metabolic clearance, increased oxidative stress, and a higher rate of RCO formation are synergistically responsible for the high concentrations of AGEs found during chronic renal failure.

**AGEs AND RECEPTOR-INDEPENDENT EFFECTS ON MATRIX PROTEINS**

Carbonyl-modified proteins may have direct, receptor-independent pathological effects depending on the site of their generation. AGE-degenerated proteins may profoundly alter the structural, mechanical, and functional properties of the affected tissues. Cross-linking by AGEs has been noted for collagen molecules under a variety of pathological conditions, which, on multiplying their cross bridges, increase their biomechanical stiffness and brittleness. This feature, for instance, has profound implications for vascular wall elasticity and the development of arterial hypertension and its complications such as stroke (21, 158). AGE-modified collagen molecules have been implicated as an important pathogenic factor during subcutaneous skin aging. When the composition of glomerular extracellular matrix and capillary basement membrane is affected, organ dysfunction and failure may follow at an accelerated rate (36, 138). Such AGE-modified structural proteins can interfere with normal cell-matrix contact or inhibit physiological cellular growth and intercellular contact that are necessary to maintain tissue integrity and normal function. Endothelial cells may become insensitive to exogenous stimuli and develop abnormal growth patterns (12, 49). Albumin is one of the main targets of AGE modification in plasma. Its glycation, for instance, induces abnormal refolding of its three-dimensional structure, conformational rearrangement of amino acids into β-sheets and a cross-β structure characteristic of amyloid fibrils may result from this process as evidenced by transmission electron microscopy. Such glycated albumin subsequently is prone to condensate into amorphous fibrous aggregates while losing its innate biochemical properties (15). Another protein with a similar fate is β2-microglobulin (18). Local deposits of amyloid albumin condensates may be resistant to removal by macrophages and promote inflammation.

Pathological aggregates of AGE proteins may exhibit insensitivity to matrix metalloproteinase degradation, thereby causing abnormal extracellular matrix turnover or fibrous expansion of the interstitial space, with progressive scarification (93). AGE formation, nevertheless, is not restricted only to extracellular proteins accessible to circulating oxidative or carbonyl stress but has been also shown to occur intracellularly. Giardino et al. (44), for instance, showed that intracellular basic fibroblast growth factor produced by endothelial cells may rapidly undergo AGE modification following cytosolic oxidative stress, thereby changing its growth factor properties and reducing mitogenic cellular activity. Other cytokines and cellular proteins may similarly lose their intrinsic biological activity as a result of AGE modification. Intracellular AGE formation, finally, corresponds directly with hyperglycemia-induced intracellular oxidative stress and increased mitochondrial superoxide generation. As a result, methylglyoxal production is induced intracellularly, being the major AGE-forming reaction partner within endothelial cells. As a consequence, intracellular AGE concentrations rise progressively with critical damage of vital proteins and cellular structures while causing cellular dysfunction (45, 99, 124). Another serious side effect is genomic DNA damage following intracellular carbonyl stress (133). This important intracellular AGE-generating pathway is operative independently of receptor-mediated effects and appears as a crucial pathophysiological step in AGE-associated renal and vascular damage in diabetes. Based on this concept, promising new pharmacological interventions to interrupt this intracellular sequence of events have been proposed recently (47). Similarly, angiotensin can induce intracellular oxidative stress via activation of its angiotensin type 1 receptor (AT1R).

In a transgenic rat model with chronic angiotensin-induced renal damage, we were recently able to demonstrate AGE formation and accumulation of CML in glomeruli, particularly within the outer glomerular linings under nondiabetic conditions (see Fig. 4) (2, 13). Our findings extend those by Nishikawa et al. (99) and others (163) and lend support to the hypothesis that oxidative stress and subsequent AGE generation may also be involved in angiotensin-dependent end-organ damage as one common final pathway.

**AGEs IN THE KIDNEY**

AGE accumulation in the kidney may follow quantitative trapping of AGEs from the circulation or result from either local generation of new AGEs involving preexisting proteins or pathologically decreased AGE turnover. Figure 2 gives an example of the histological distribution of AGEs in the kidney in a patient with advanced diabetic nephropathy. The process of renal trapping of AGEs has been evidenced by chronic intravenous infusion of AGE (CML)-modified rat albumin into normal rats. After 5 mo of infusion, the AGE content of the kidneys increased by 50% in treated compared with control animals and histological features similar to diabetic glomerulosclerosis, with basement membrane widening, increased glomerular tuft volume, mesangial extracellular matrix expansion, glomerulosclerosis, and albuminuria, were present (148). This mouse infusion model had been initially described by McVerry et al. (94) as producing a pseudodiabetic renal pattern. In the experiment by Vlassara et al. (148), total serum AGE concent-

![Fig. 2. AGE staining for imidazolone in a renal specimen from a patient with advanced diabetic nephropathy with glomerulosclerosis. Brown staining indicates imidazolone. Magnification: ×400.](http://ajprenal.physiology.org/)
trations about twofold above those observed in human diabetes were achieved. The model, however, lacks elevated serum glucose concentrations and the typical metabolic features of diabetes. Furthermore, AGE albumin was administered to mice with normal renal function, thereby reflecting the reaction of normal kidneys to a chronic toxic stimulus. The lesions in diabetic nephropathy and chronic renal failure of other origin, however, evolve over time as a result of complex pathophysiological mechanisms, with different cellular pathways usually operative in parallel. For instance, exposure to high glucose itself may alter cellular function in the absence of AGES. Also, the release of cytokines or activation of local homeostatic systems such as the renin-angiotensin system independently of AGE stimulation has its own established pathogenetic role (2). Nevertheless, the AGE infusion model and similar models of chronic renal injury may provide helpful insight into important pathogenetic aspects, for instance, associated with circulating AGE proteins despite their inherent limitations. Interestingly, inhibition of albumin glycation in a complementary in vivo model of diabetic db/db mice has recently been shown to ameliorate glomerular and indexes of renal end-organ damage, supporting a pivotal role of circulating AGE compounds (26, 27). In humans, renal and vascular accumulation of AGE is most prominent in diabetes mellitus, where global AGE generation occurs early and at an accelerated rate in almost any organ system. Glomerular and vascular AGE accumulation has been shown to be a major pathogenic factor precipitating diabetic vascular complications and glomerulosclerosis (72, 152).

Diabetic nephropathy is characterized by glomerular and tubular basement membrane thickening, mesangial extracellular matrix expansion, microvascular damage, and fibrotic changes in the tubulointerstitium. Almost all renal structures are susceptible to accumulate AGES including basement membranes, mesangial and endothelial cells, podocytes, and tubules (46). Horie and colleagues (53) examined in detail the immunohistochemical localization of glycoxidation products in glomerular lesions and in the vasculature of patients with early compared with advanced diabetic nephropathy. They found enhanced CML accumulation in the expanded mesangial matrix, thickened glomerular capillary wall of early nodular lesions, and also in arterial walls of advanced diabetic nephropathy but not in normal kidneys. Niwa et al. (100) showed similar results for imidazolone. This observation could also be replicated experimentally in genetically or streptozotocin-treated diabetic rats (65, 153). Nondiabetic nephropathies, however, may display different patterns of local AGE distribution. Kidney sections from patients with IgA nephropathy, for instance, do not show glomerular CML accumulation or staining for acrolein. Rather, the glomerular matrix lesions stained positive for reactive lipoxidation products such as malondialdehyde-lysine, implicating fundamental pathophysiological differences (138). Another study by Tanji et al. (141) of renal tissue specimens from patients with diabetic nephropathy, primary and secondary focal segmental glomerulosclerosis type, hypertensive nephropathy, and lupus nephritis showed significant qualitative and quantitative differences in the distribution of CML and pentosidine, respectively, demonstrating an independent influence of the disease mechanism and the course of the disease on the type of AGE modification and the distribution of AGE-modified structures.

**RECEPTOR-MEDIATED EFFECTS ON CELLULAR FUNCTION**

The presence of AGE-modified proteins in tissues, the biological effects associated with their accumulation, and pharmacological inhibition studies have stimulated intensive research to identify cellular surface molecules that recognize AGES and may induce specific cellular responses. In 1992, Schmidt and her colleagues (98, 119) first discovered a cellular surface receptor that binds AGE-modified proteins with high affinity, which was subsequently termed RAGE. Continuous research has meanwhile identified several other receptors and cell surface molecules capable of binding AGE-modified proteins. These receptors include macrophage scavenger receptors (MSR) type A and B (CD36), oligosaccharyl transferase-48, termed AGE receptor 1 (AGE-R1), 80K-H phosphoprotein (AGE-R2), and galec-tin-3 (AGE-R3) (67, 90, 103).

Among these AGE-binding receptors, RAGE has been best characterized. It is a 35-kDa protein belonging to the immunoglobulin superfamily. Accordingly, its gene has been located on chromosome 6, between the genes for major histocompatibility complex II and III (120, 134). Cloning experiments and molecular characterization have revealed its three-dimensional structure and elucidated its functional properties (Fig. 3). RAGE is a transmembrane receptor consisting of 394 amino acids with a single hydrophobic transmembrane domain of 19 amino acids and a COOH-terminal cytosolic tail of 43 amino acids and shares homology with MUC 18, NCAM, and, partly, CD20, a B-cell activation marker (98). The extracellular part consists of a terminal V-type and two distinct C-type domains (V-C-C'), where V domains bind ligands and the highly charged cytosolic tail would mediate activation of intracellular signal transduction pathways. Because of its short cytosolic tail without apparent enzymatic activity, it has been speculated that the receptor may associate into a multimeric cell surface complex on activation before triggering cellular events involving other costimulatory proteins (160). Various viable mRNA splice variants have been detected encoding for truncated proteins with different biological properties. RAGE lacking the cytosolic tail remains anchored within the cell membrane and binds extracellular ligands without intrinsic effects but can suppress cellular signaling by full-length RAGE in a dominant-

![Fig. 3. Structure of the receptor for advanced glycation end products (RAGE) and major splice variants. The molecule has 3 extracellular domains (V-C-C') where the V-domain interacts with ligands. TMD, transmembrane domain; ct, cytosolic tail; DN-RAGE, dominant-negative RAGE; ES-RAGE, endogenous soluble RAGE; NT-RAGE, N-truncated RAGE.](http://ajprenal.physiology.org/)

neurons, microglia, astrocytes, and peripheral nerves, the cells, and macrophages but also in neural tissues such as vascular smooth muscle cells, peripheral blood mononuclear variety of tissues. The receptor is found on endothelial cells, does not bind ligands with a still unclear role (73, 167). V-domain has been found that resides in the cell membrane but larly secreted. Finally, a version lacking the NH2-terminal domain serving as an anchor sequence and therefore is simi-
isoform lacks only the small 19-amino acid transmembrane receptors located in the cell membrane. Still another RAGE thereby possibly preventing epitope recognition by full-length possibility of AGE modification of proteins. Rather, this may be an extended ability based on its natural function as a modulator of inflammatory processes. Recent research has identified S100/calgranulins as unexpected new ligands with distinct pathophysiological properties on binding RAGE. The S100/calgranulins are a family of Ca\(^{2+}\)-binding polypeptides with >20 yet identified members. Some members of the group including S100A8, S100A9, and S100A12 (calgranulin C) are released by stimulated phagocytes and may act as secretory cytokines. These S100 molecules have been shown to activate endothelial cells, mononuclear phagocytes, and lymphocytes on binding RAGE while inducing multiple proinflammatory responses, for instance, increased cyclooxygenase (COX)-2 expression (52, 111, 122). Stimulation of RAGE by S100P can directly induce cellular proliferation (8). Using a mouse model of peritonitis, administration of soluble RAGE and investigat-
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leagues (24) showed that leukocyte adhesion and extravasation were tightly controlled by RAGE. The effect was independent of ICAM-1, the principal ligand for leukocyte adhesion (24). These evolving new features characterize RAGE as a versatile multiligand receptor intrinsically involved in amplifying and maintaining inflammatory responses as well as modulating cellular function and growth in response to a variety of extracellular stimuli or environmental inflammatory cytokines.

In the presence of extracellular AGE, susceptible cells can rapidly upregulate expression of RAGE. In the kidney, this effect has been consistently demonstrated for glomerular podocytes in diabetic nephropathy. In contrast, RAGE expression in other glomerular cells is generally less inducible (130, 141, 153). Furthermore, cellular expression of RAGE can be induced by AGE ligands themselves. Its expression, however, can also increase in the absence of AGEs, for instance, during inflammatory tissue remodeling or after direct cytokine stimu-
lation by TNF-\(\alpha\) (6, 115, 140). These observations are readily explained by the presence of NF-\(\kappa\)B and SP-1 binding sites in the promoter region of the RAGE gene (68). In an animal model of amyloidosis, mononuclear phagocytes invading \(\beta_2\)-amyloid-containing plaques upregulated RAGE expression and released TNF-\(\alpha\).

Fig. 4. Glomeruli from transgenic rats with ANG II-dependent hypertension (A) and nontransgenic controls stained immunohistochemically for CML (B). Note the positive staining for AGE in transgenic glomeruli along the outer capillary loops (brown stain). Magnification: \(\times 400\).

Physiological expression of RAGE has been detected in a variety of tissues. The receptor is found on endothelial cells, vascular smooth muscle cells, peripheral blood mononuclear cells, and macrophages but also in neural tissues such as neurons, microglia, astrocytes, and peripheral nerves, the lungs, and skeletal muscle (19, 56, 129, 130). In the human kidney, physiological RAGE expression of RAGE protein was found only on podocytes at a very low concentration. Its expression, however, could not be detected in other glomerular cell types. In contrast, tubular epithelia may stain positive for RAGE (130, 141). The receptor has been shown to bind different AGE adducts nonspecifically. Among these, CML and pentosidine adducts are high-affinity ligands (62). RAGE therefore may bind and recognize different proteins alike, independently of their individual biological function, which suggests a biological role as a nonspecific environmental sensor. In this context, RAGE can be characterized as a pattern- or common motif-recognizing receptor with homeostatic functions accepting diverse epitopes independently of their location and mode of presentation, much like other members of its superfamily. Therefore, amyloid-\(\beta\) protein is similarly recognized as are other proteins, for instance, amylin, serum amyloid A, albumin, prion-derived peptides, and \(\beta_2\)-microglobulin, after glycation and conformational rearrangement of their three-dimensional structure (15, 79, 164). The receptor’s role, however, is not restricted to the pathological situation of AGE modification of proteins. Rather, this may be an extended ability based on its natural function as a modulator of inflammatory processes. Recent research has identified S100/calgranulins as unexpected new ligands with distinct pathophysiological properties on binding RAGE. The S100/calgranulins are a family of Ca\(^{2+}\)-binding polypeptides with >20 yet identified members. Some members of the group including S100A8, S100A9, and S100A12 (calgranulin C) are released by stimulated phagocytes and may act as secretory cytokines. These S100 molecules have been shown to activate endothelial cells, mononuclear phagocytes, and lymphocytes on binding RAGE while inducing multiple proinflammatory responses, for instance, increased cyclooxygenase (COX)-2 expression (52, 111, 122). Stimulation of RAGE by S100P can directly induce cellular proliferation (8). Using a mouse model of peritonitis, administration of soluble RAGE and investigat-
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shall focus here on the contributions of the AGE-RAGE axis to this process. A main feature of diabetic glomerulosclerosis is excess accumulation of extracellular matrix leading to mesangial matrix expansion as well as glomerular basement membrane thickening, which then becomes targeted by AGE modification. At a cellular level, release of TGF-β is the main trigger of this process (172). Early in the course of the disease, mesangial cells may undergo a phase of limited proliferation, but then they typically arrest in the G1 phase of the cell cycle to produce extracellular matrix (156). In an animal model, these cellular and molecular events typical for progressive diabetic nephropathy can be partially mimicked, for instance, by chronic intravenous infusion of CML-albumin (148, 165). Furthermore, mesangial cells exposed to AGE-albumin at concentrations comparable to those found in human pathology showed increased collagen IV and TGF-β expression as well as activation of protein kinase C (28, 29, 118). Yamagishi and colleagues (161) showed that AGES stimulated upregulation of p53 and Bax by mesangial cells in vitro, thereby facilitating apoptotic cell death. The mesangial cells also produced VEGF and monocyte chemotactic protein-1, which stimulated prostatic cyclin production by cocultured endothelial cells. This pathophysiological sequence may serve as a model for the events leading to chronic glomerular injury in the diabetic kidney in vivo.

Interestingly, cultured glomerular endothelial cells were similarly shown to release TGF-β after exposure to glycated albumin, which may conversely lead to paracrine stimulation and recruitment of adjacent mesangial cells (20, 25, 157, 173). Endothelial cells exposed to AGES may rapidly show signs of enhanced cellular oxidant stress (163). AGE-albumin or CML can also induce connective tissue factor growth factor (CTGF) expression in mesangial cells, a cytokine that stimulates extracellular matrix synthesis and functions as an important downstream mediator of TGF-β but may occur without it (144, 170). Mesangial cells also express inducible macrophage scavenger receptor, which binds AGES independently from RAGE and thereby possibly facilitates transformation of mesangial cells into foam cells (112). Geoffroy et al. (43) described in vitro proliferation of mesangial cells exposed to AGES and defined a role for intracellular ceramidase and sphingolipids to control this effect. Finally, inhibition of store-operated Ca2+ influxes by AGE-modified bovine serum albumin has been described in mesangial cells that may explain their abnormal contractile properties observed in diabetes (76).

Albuminuria is a prominent feature of progressive diabetic glomerular damage. Vascular permeability and proteinuria have been directly associated with VEGF and its dimeric transmembrane tyrosine kinase receptor (VEGFR). VEGF may induce increased endothelial fenestration, decreased molecular selectivity, and plasma exudation at the endothelial vascular border. VEGF’s principal physiological expression site is the podocyte, whereas its receptor (VEGFR-2) is predominantly expressed on glomerular endothelium. In diabetic nephropathy, renal expression of RAGE increases considerably together with the expression of VEGF and VEGFR-2, which parallels glomerular capillary AGE deposition and AGE modification of the capillary basement membrane. In particular, podocytes upregulate their RAGE and VEGF expression in the chronic course of diabetic nephropathy (30, 61, 126). In vitro podocyte upregulation of RAGE expression can be observed, for instance, after

Activation of RAGE finally triggers multiple intracellular signal transduction cascades depending on the individual cell type. Interaction of AGES with RAGE, their cellular receptor, may result in enhanced intracellular oxidant stress and activation of NF-κB by redox-sensitive signaling pathways (163). AGES may also inhibit cellular NO production, which is mediated, at least in part, by downregulation of NO synthase and increased NADPH oxidase expression linking RAGE to chronic endothelial cell dysfunction (17, 110, 150). RAGE-triggered activation of NF-κB may confer a susceptible state by upregulation of RAGE itself via its promoter’s own NF-κB binding site, thereby enhancing cellular capacity to bind AGES. RAGE activation was shown to stimulate RAGE mRNA transcription directly and thus may initiate an autoamplifying loop during cell activation (68, 140). As a consequence, cells activated by RAGE may release a host of cytokines and growth factors to recruit other adjacent cells into the inflammatory reaction. The receptor’s cellular actions are summarized in Table 2. RAGE activation was finally shown to induce intracellular generation of hydrogen peroxide, which was dependent on the functional integrity of NADPH oxidase. The signaling cascade involves p21^{ras}, p38, protein kinase C, and mitogen-activated protein kinases (MAPK) including Erk 1/2 (p44/p42) (25, 64, 150, 166). In mesangial fibroblasts, RAGE-mediated signals have been shown to converge also on STAT5 and p21^{ras} to control the cell cycle (21).

**Table 2. Cytokines and cellular events associated with AGE or RAGE activation**

<table>
<thead>
<tr>
<th>Cytokine or event</th>
<th>Cells and context</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCAM-1 ↑</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>ICAM-1 ↑</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>E-selectin ↑</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>PDGF ↑</td>
<td>Pancreatic cancer cells</td>
</tr>
<tr>
<td>Tissue factor ↑</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>TGF-β ↑</td>
<td>Mesangial cells, proximal tubular cells, vascular smooth muscle cells, macrophages</td>
</tr>
<tr>
<td>TNF-α ↑</td>
<td>Endothelial cells, mesangial cells, mononuclear macrophages</td>
</tr>
<tr>
<td>IGF-1 ↑</td>
<td>Mesangial cells</td>
</tr>
<tr>
<td>MCP-1 ↑</td>
<td>Mesangial cells, endothelial cells</td>
</tr>
<tr>
<td>CTGF ↑</td>
<td>Fibroblasts, mesangial cells</td>
</tr>
<tr>
<td>IL-6 ↑</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>PAI-1 ↑</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>RAGE ↑</td>
<td>Mesangial cells, endothelial cells, podocytes</td>
</tr>
<tr>
<td>VEGF ↑</td>
<td>Podocytes, endothelial cells, mesangial cells</td>
</tr>
<tr>
<td>ANG II-dependent cell activation ↑</td>
<td>Vascular smooth muscle cells</td>
</tr>
<tr>
<td>Type IV collagen expression ↑</td>
<td>Mesangial cells</td>
</tr>
<tr>
<td>Fibronectin ↑</td>
<td>Mesangial cells</td>
</tr>
<tr>
<td>Cell cycle progression ↓</td>
<td>Fibroblasts, mesangial cells</td>
</tr>
</tbody>
</table>

eNOS, endothelial nitric oxide synthase; TGF-β, transforming growth factor-β; MCP-1, monocyte chemotactic protein-1; CTGF, connective tissue growth factor; PAI-1, plasminogen activator inhibitor-1.

In the diabetic kidney, progressive tissue damage is closely related to the local deposition of AGES and its pathophysiological consequences. The mechanisms leading to chronic diabetic nephropathy are complex, however, involving the renin-angiotensin system as well as many other proinflammatory cytokines and signaling pathways in parallel (121). We
stimulation with calgranulin S100B. Treatment of diabetic rats with antibodies against VEGFR-2 and infusion of soluble RAGE (sRAGE) into diabetic db/db mice significantly reduced albuminuria and glomerular hypertrophy. In addition, chronic treatment of diabetic mice with sRAGE prevented abnormal renal endothelial permeability. On the other hand, homozygous RAGE null mice rendered diabetic did not develop increased renal VEGF antigen and mRNA expression as well as renal TGF-β mRNA expression compared with their nondiabetic counterparts, indicating a pivotal role for RAGE and VEGF in this process (35, 153).

After being filtered by the glomerulus, AGE peptides can be readily absorbed by proximal tubular cells. Tubular cells are sites of RAGE expression that may be actively involved in cellular AGE uptake such as megalin, another tubular receptor. In diabetic nephropathy with proteinuria, proximal tubular cells were shown to display increased NF-κB activation. This effect could be suppressed experimentally by simultaneous administration of soluble RAGE (80, 92, 114). Similarly, after exposure to an AGE-rich extracellular milieu, cultivated tubular cells showed upregulation of TGF-β mRNA expression, which was mediated by intracellular release of ROS (159, 161). These observations were recently extended by the discovery of TGF-β-independent tubular epitheial myofibroblast transdifferentiation initiated directly by RAGE activation (69). This process may be important for the development of tubular atrophy and interstitial fibrosis during diabetic nephropathy.

Although evidence is now growing that RAGE is a key pathogenic factor involved in endothelial cell activation, vascular wall remodeling, and neointimal expansion in diabetic vascular disease as well as in non-diabetic atherosclerosis and arterial plaque formation, relatively little is known about RAGE and its role in glomerular endothelial cells (11). RAGE expression by glomerular endothelial cells was found only under pathological conditions (1). RAGE can trigger endothelial cells to produce interleukin-6, monocyte chemotactic protein-1, induce expression of adhesion molecules, and cause intracellular generation of ROS partly by activation of NADPH oxidase with a concomitant decrease in endothelial NO synthase expression. Because endothelial cells are easily accessible to AGE-modified plasma proteins, local AGE deposition or modification of resident matrix proteins is not an obligatory prerequisite to trigger these events (110, 151, 171). At a cellular level, a synergistic effect of RAGE on ANG II-dependent activation of vascular smooth muscle cells has been described (84). Interestingly, acute hyperglycemia for as short as 2 h in humans produced by a glucose-clamping technique was capable of inducing intracellular generation of CML and activating NF-κB in peripheral blood mononuclear cells (118). Such concomitant effects may be important steps during endothelial cell activation in the presence of AGEs.

Among the many other AGE-binding proteins, the pathophysiological importance of AGE-R3 (galectin-3) and its congener AGE-R1 and AGE-R2 is now increasingly recognized. Galectin-3 has been deleted in a knockout mouse model. In contrast to similar RAGE knockout animals, these mice spontaneously develop glomerulosclerosis with increased proteinuria on aging (109). Functionally, galectin-3 interacts closely with AGE-R1 and AGE-R2 within a molecular aggregate on cellular surfaces termed the “AGE receptor complex.” The biology of this receptor complex is not yet completely understood. For instance, cultured endothelial cells readily upregulate AGE-R2 and -R3 on exposure to AGE proteins (127). In an experiment with diabetic rat kidneys, however, galectin-3 (AGE-R3) expression started to increase only about 2 mo after induction of diabetes and later, during the course of the disease, galectin-3 is involved in endocytotic activity and may actively remove AGE proteins or AGE-modified LDL. The molecule obviously exerts protective cellular effects with an aim to modulate or to contain AGE-dependent inflammatory or noxious reactions (57, 147). This notion is supported by a recent report demonstrating a negative regulatory effect of AGE-R1 on AGE-dependent proinflammatory responses in mesangial cells (71). The AGe receptors are differentially regulated during diabetic kidney disease. In contrast to RAGE, AGE-R1 was found to be downregulated, thereby decreasing its overall cytoprotective potential (50). Together, these results point to an important synergism of this group of alternative AGE binding proteins with an aim to counteract or modulate the deleterious effects of the AGE-RAGE interaction.

**GENETIC ASPECTS OF RAGE**

A variety of polymorphisms of the human RAGE gene have been identified and studied for their impact on disease development. The gene proved to be highly variable, bearing many single nucleotide polymorphisms with potential phenotypic effects. Hudson et al. (54, 55) described a −429T/C in the gene’s promoter region and presented data suggesting an association of the −429C allele with diabetic retinopathy in type 2 diabetes with macrovascular disease. Recently, Rudofsky and co-workers (113) reported that a 63-bp deletion in the promoter of RAGE correlates with a decreased risk for nephropathy in patients with type 2 diabetes, but not in individuals with type 1 diabetes.
Other ACE-inhibitors, AT1-receptor blockers, and aldosterone antagonists may help to reduce AGE-associated end-organ damage. Investigational compounds are also being used to prevent AGE formation or accumulation and to serve as adjunctive therapy in the specific treatment of diabetes or cardiovascular disease. Preventive strategies may be preferable to clinicians as an alternative to current therapies, especially in patients with diabetes. Tiamine similarly intervenes at a cellular level (47). This vitamin helps by trapping reactive carbonyl intermediates based on their nucleophilic potential or quench ROSr and oxidative stress. Benfotiamine similarly intervenes at a cellular level (47). This preventive strategy may be preferable to clinicians as an adjunctive therapy in the specific treatment of diabetes or chronic renal failure, delaying progressive end-organ damage. In advanced disease, compounds reducing AGE deposition or breaking established protein cross-links may become the first choice. Finally, drugs preventing AGE-induced cellular activation, for instance, inhibitors of RAGE, could be a supportive therapy, whenever inflammatory reactions should be controlled. Dietary options, instead, could possibly become an attractive nonpharmacological alternative (23).

I diabetes. Finally, a relationship between the A-374A polymorphism and angiographic coronary artery disease has recently been noted, with a lower frequency of the A allele in affected compared with disease-free subjects (37).

PHARMACOLOGICAL INTERVENTIONS

A variety of pharmacological compounds and strategies have been studied in vitro as well as in vivo for their potential to prevent AGE formation or local AGE accumulation. A detailed analysis of the current literature is provided by recent topical reviews (10, 75, 154). These drugs can be divided into different classes according to their mechanism of action (Fig. 5). For instance, substances may reduce the amount of already formed AGES by chemically reopening AGE-mediated cross-links between proteins, thereby reducing or neutralizing established end-organ damage by AGES in the vasculature or kidney. Alagebrum is such a new prototypic compound that reduces renal AGE content in animal models and humans (10). Alagebrum is such a new prototypic compound that reduces renal AGE content in animal models and humans (10).

Table 3. Investigational compounds used to prevent AGE formation or accumulation and to reduce AGE-associated end-organ damage

<table>
<thead>
<tr>
<th>Class</th>
<th>Compound</th>
<th>Mode of Action</th>
<th>Animal Study(ies)</th>
<th>Clinical Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitor of AGE (ALE) formation</td>
<td>Aminoguanidine (Pimagedine)</td>
<td>Nucleophilic agent; reaction with glucose-derived intermediates, e.g., α,β-dicarbonyl compounds (143)</td>
<td>Renal profibrotic cytokines ↓, collagen IV ↓, protein carbonylation ↓, albuminuria ↓, prevents activation of protein kinase C; aortic stiffening ↓ (60, 70, 106, 168)</td>
<td>Bolton et al. (14)</td>
</tr>
<tr>
<td>Pyridoxamine (Pyridorin)</td>
<td>Post-Amadori reaction inhibitor (Amadorin), carbonyl trapping, chelation of catalytic metal ions, inhibits superoxide radicals (5, 58, 78, 149)</td>
<td>Lipid-lowering effect, inhibits progression of diabetic nephropathy, albuminuria ↓, cross-linking of collagen n ↓ (4, 33)</td>
<td>Williams et al. (155)</td>
<td></td>
</tr>
<tr>
<td>OPB-9195, ALT-946</td>
<td>Carbonyl trapping (86) Inhibits protein cross-linking</td>
<td>Renal AGE accumulation ↓ (96) Renal AGE accumulation ↓ (38) Large artery stiffness ↓, improved ventricular function, inhibits renal fibrosis, proteinuria ↓, inhibits activation of PKC-α, profibrotic cytokines ↓, oxidative stress ↓, cellular transdifferentiation ↓, renal AGE content ↓ (40, 65, 105, 137, 142, 158)</td>
<td>Miyata et al. (86)</td>
<td></td>
</tr>
<tr>
<td>Cross-link breaker</td>
<td>Alagebrum (ALT-711)</td>
<td>Opens AGE-derived protein cross-links (136) Vascular AGE accumulation ↓ (31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGE neutralization</td>
<td>N-phenacylthiazolium bromide (PTB)</td>
<td>Opens AGE-derived protein cross-links</td>
<td>AGE accumulation ↓, AGE clearance ↑ (27, 70, 169) Plasma and renal AGE accumulation ↓ (39, 117)</td>
<td>Sebekova et al. (116)</td>
</tr>
<tr>
<td>Other</td>
<td>Soluble receptor of AGE, AGE-antibodies, lysozyme</td>
<td>Inhibits biological actions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitors, AT1-receptor blocker</td>
<td>Thiazolidinediones</td>
<td>Receptor of AGE expression ↓ (74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td></td>
<td>AGE-induced angiogenesis ↓ (104)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.
beneficial effects. Patients with nondiabetic nephropathy treated for 2 mo with an angiotensin-converting enzyme (ACE) inhibitor showed a moderate decrease of plasma AGE concentration in parallel with improved parameters of oxidative stress. Furthermore, treatment with an angiotensin type 1-receptor antagonist prevented the modest rise of AGE concentrations in a renal ablation model (116, 117). Similarly, olmesartan significantly reduced renal pentosidine content in a hypertensive diabetic rat model (97). Interestingly, AT1-receptor antagonists and ACE inhibitors may lower the generation of serum AGES in a cell-free in vitro system (88).

SUMMARY AND FUTURE DIRECTIONS

Formation of AGES is an ubiquitous slow process of protein modification and degeneration by sugar molecules and reactive intermediates of oxidant and carbonyl stress that occurs in situations where the biochemical reaction equilibrium is shifted toward covalent interaction between the two reaction partners. This effect is most prominent in diabetes mellitus and chronic renal failure characterized by uremic carbonyl stress when considerable amounts of AGE-modified proteins accumulate in plasma and tissues. In the kidney, AGES and RAGE, their main receptor, are intrinsically involved in accelerating diabetic and uremic glomerulopathy with tubulointerstitial damage. Furthermore, nonreceptor-mediated intracellular AGE generation initiated by mitochondrial superoxide release plays an independent role in diabetes. The pathophysiologic implications of AGES, RAGE, and other AGE binding proteins are rapidly expanding, whereas their role in vascular remodeling, chronic inflammatory processes, and cellular dysfunction becomes increasingly recognized.

Despite these advances, however, many important aspects of AGES and their role in renal biology still remain unclear. For instance, the interactions of other homeostatic systems involved in renal pathology such as the renin-angiotensin, NO, or the endothelin systems with the AGE-RAGE axis are not well understood. Studies will therefore have to dissect the relative contributions of each system to oxidative stress, AGE generation, and AGE receptor-mediated or -independent events. With potent inhibitors available, future in vivo studies should address the relevance of the many in vitro findings using also transgenic and nondiabetic animal models to further extend our knowledge beyond classic metabolic pathways. In this context, the renin-angiotensin system is a primary candidate given its clinical importance as a target for therapeutic interventions to slow the progression of chronic renal failure (42). Finally, in view of the limited effects of drug therapy or dialysis modalities on AGE accumulation in end-stage renal failure due to the longevity of established AGE proteins, particular emphasis should be put in the future on preventive pharmacological strategies and early stages of renal damage. Less toxic compounds are required, and the development of a synthetic RAGE inhibitor could be of interest. Such human studies could also include combination therapies to exploit synergistic effects.

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Advanced glycation end products (AGEs) and the kidney

Invited Review

AGES AND THE KIDNEY

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