Angiotensin-Converting Enzyme Inhibition in Diabetic Nephropathy: It's All the RAGE

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Since the landmark multicenter trial in type I diabetics by Lewis *et al.* in 1993 (1), the use of angiotensin-converting enzyme (ACE) inhibitors to retard progression of diabetic nephropathy has become a widely accepted therapeutic strategy. Although initial animal studies determined that ACE inhibitors decrease the increased glomerular capillary pressure (P_{GC}) associated with the hyperfiltration of diabetes (2,3), more recent studies have also attributed to angiotensin II many pathogenic changes observed in the glomerulus and tubulointerstitium in diabetes that are not necessarily related to altered intrarenal hemodynamics, including production of reactive oxygen species, cytokine and growth factor release, and alterations in extracellular matrix production. Recently, a number of studies have also indicated that drugs that interfere with the renin-angiotensin system may also decrease levels of advanced glycation endproducts (AGE) (4–6).

Although diabetic nephropathy is likely to have a multifactorial etiology (7) and to be subject in part to genetic predisposition, there is increasing evidence that AGE play an important role in its development. In the setting of diabetes mellitus and long-term hyperglycemia, free amino groups of proteins are nonenzymatically modified by glucose and its metabolites to form Schiff bases, which then rearrange to form Amadori products. Further modification by the Maillard reaction, nonenzymatic glycation, leads to formation of AGE. The most commonly formed AGE include N-ε-(carboxymethyl)lysine (CML), pentosidine, pyrraline, and imidazolone (8–12).

AGE may induce functional changes through nonreceptor-mediated pathways by crosslinking proteins, such as basement membrane. In addition, a number of AGE-binding proteins have been identified, including galectin-3, macrophage scavenger receptors, p60 complex, and p90. The best-described binding protein is receptor for advanced glycation endproducts (RAGE). RAGE is a member of the Ig superfamily of cell surface molecules (13) and is composed of a large N-terminal extracellular portion of 332 amino acid residues consisting of a distal V-type Ig domain, followed by two C-type Ig domains; ligands interact with the V-domain of the receptor (14–16). CML-adducts are a major class of AGE that bind to RAGE (17,18).

Following ligation of the extracellular region, transmembrane signaling by RAGE is thought to be transduced by the single hydrophobic transmembrane-spanning domain and short cytosolic tail. The intracellular portion of the molecule is essential for RAGE-triggered signaling and activates NF-κB coupled signaling (17,18) as well as Cdc42-Rac-1-MKK6-p38 mitogen-activated protein kinase (MAPK) pathways (19,20). Binding of AGE to RAGE activates cell signaling mechanisms coupled to increased TGF-β and vascular endothelial growth factor (VEGF) expression that are thought to contribute to the pathogenesis of diabetic complications (16,21).

In this issue of *JASN*, Forbes *et al.* undertook studies investigating the potential mechanism underlying the observation that treatment with ACE inhibitors can decrease levels of circulating and tissue AGE (22). Previous *in vitro* studies by Miyata *et al.* had determined that direct incubation of diabetic serum with any of six angiotensin II type 1 receptor (AIIR) antagonists or four ACE inhibitors inhibited the formation of both pentosidine and CML, with angiotensin receptor blockers (ARB) being somewhat more effective (5). In a rat model of type II diabetes, Nangaku *et al.* further reported that ARB, as well as hydralazine, could decrease kidney pentosidine content (6). In contrast, in both the current as well as former studies by Forbes and coworkers, there was a selective decrease of CML AGE in response to treatment with ACE inhibitors (4,22). These observations were confirmed in cell culture, in experimental animals, and in humans with incipient nephropathy secondary to type I diabetes. This selective decrease in CML and not pentosidine suggested a role for RAGE.

Recent studies have determined that three isoforms of RAGE are expressed through alternative splicing: the full-length transmembrane receptor, a soluble truncated form containing only the extracellular domain (sRAGE), and a truncated isoform containing the transmembrane and cytoplasmic portions of the receptor (N-truncated RAGE) (23). In their current studies, Forbes *et al.* determined that in poorly controlled diabetes, expression of the full length and N-truncated RAGE isoforms increased, while with ACE inhibitor treatment expression and secretion of sRAGE was selectively increased.

This study raises many interesting questions. What is the relationship between the ACE inhibitor-induced increases in sRAGE expression and decreases in circulating and tissue AGE, *i.e.*, is the selective upregulation of sRAGE a cause or effect of decreased circulating AGE? ACE inhibitors can

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decrease tissue oxidative stress, and there is evidence that inhibition of free radical production may decrease AGE production (5). Furthermore, there is some evidence that AGE may directly upregulate full-length RAGE (24). In these studies, administration of a mitochondrial reactive oxygen species scavenger to endothelial cells *in vitro* did lead to an increase in sRAGE secretion. Conversely, previous studies indicated that administration of sRAGE prevented diabetic atherosclerotic lesions and diabetic nephropathy in experimental animals (25) (16), and in their studies, Forbes *et al.* were able to identify circulating sRAGE/CML-AGE complexes.

These studies also did not determine whether the ACE inhibitor effect on sRAGE is the result of inhibiting angiotensin II–mediated signaling and, if so, the mechanism by which angiotensin II increases RAGE expression. Against a direct role for angiotensin II in these responses is the finding by Forbes *et al.* in their *in vitro* studies that the ARB valsartan did not increase sRAGE secretion; however, no *in vivo* studies were performed with ARB. If the effect on sRAGE expression does prove to be specific for ACE inhibitors, further studies will be necessary to determine whether it is a class effect, because only two ACE inhibitors (ramipril and perinopril) were used in these studies. If it is a class effect, is it secondary to increased bradykinin production or to some other structural characteristic of ACE inhibitors? Further studies will also be necessary to determine the biologic significance of this intriguing observation and to determine whether the ACE inhibitor-induced alterations in RAGE and AGE represent a previously unappreciated mechanism by which these drugs retard the progression of diabetic nephropathy.

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See related article, "Modulation of Soluble Receptor for Advanced Glycation End Products by Angiotensin Converting Enzyme-1 Inhibition in Diabetic Nephropathy," on pages 2363–2372.