ACE2: A New Target for Prevention of Diabetic Nephropathy?

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bundant, well-accepted evidence demonstrates a complete tissue renin-angiotensin system (RAS) within the kidney that plays many roles in the control of the intrarenal vasculature, as well in the control of glomerular and tubular processes (1). Substantial clinical and experimental data suggest that the intrarenal RAS is important, if not central, to the development and progression of diabetic nephropathy. Given the major impact of diabetic nephropathy on the health of diabetic individuals, to say nothing of health costs, alterations in the intrarenal RAS in diabetes have been of great interest, particularly given the demonstrated clinical benefit of blocking the RAS on the development and progression of diabetic nephropathy (2).

However, although the presence of an intrarenal RAS is now well-accepted, the way we think about the RAS in health and disease changed with the discovery, in 2000, of ACE2, an angiotensin-converting enzyme (ACE)-related carboxypeptidase with approximately 40% homology with ACE (3,4). Before that time, some of the so-called “breakdown products” of angiotensin I and II [Ang I; Ang II] had unknown functions, and many in the field felt that these had little or no physiologic importance. However, now our understanding about processing and breakdown of angiotensins has changed. In thinking about prevention of diabetic nephropathy, we now must consider how ACE2 might be involved.

ACE2, which preferentially removes carboxyterminal basic or hydrophobic acids, has as a major function the formation of the inactive angiotensin 1-9 from Ang I and the vasodilatory and antiproliferative angiotensin 1-7 from Ang II. In the six years since its discovery, it would appear that an overarching function of ACE2 is to counterbalance the effects of ACE, which forms Ang II (Figure 1) (5). We know that ACE2 is not responsive to ACE inhibitors (6), although we do not really know what stimulating ACE2 or inhibiting it will do clinically. The role of ACE2 in hypertension, diabetes, renal disease, and a number of other conditions is currently in the early phases of exploration.

A number of investigators have examined alterations in the expression of the various components of the intrarenal RAS during the course of diabetes. Results have been variable, as have been the species, gender, and diabetic models examined. That the intrarenal expression of ACE is altered in diabetes has been known for many years. Anderson et al. reported that, while total renal ACE was reduced in streptozotocin (STZ) diabetes in the rat, the protein appeared to be redistributed, with less in the tubules and more in the glomeruli and vasculature (7).

Intrarenal Ang II has been reported as increased, decreased, or the same as in nondiabetic control kidneys (8). The level of ACE would certainly be relevant to the amount of tissue Ang II available. In 2003, Tikellis et al. (9) reported that male Sprague-Dawley rats studied 24 wk after STZ-induced diabetes had reduced tubular expression of both ACE and ACE2, while glomerular ACE and ACE2 appeared modestly increased. More recently, Wysocki et al. (10) reported upregulation of ACE2 mRNA, protein, and activity in the kidney cortex in both the murine type 2 diabetes model (the db/db mouse) compared with control [the lean db/m mouse], and in STZ-induced diabetes, while ACE mRNA, protein, and activity were decreased, although they did not perform localization studies for either enzyme.

In this month’s issue of JASN, this same group of researchers extends its studies in a report by Ye et al. (11) that compares and contrasts the localization of ACE and ACE2 in the glomeruli of female db/db mice as compared with control lean, nondiabetic [db/m] female mice. Their localization studies are important, as they define distribution in both normal and diabetic animals. The authors note that ACE2 is primarily localized to podocyte foot processes and the parietal cells of Bowman’s capsule, whereas ACE is present in endothelial cells. They note that glomerular ACE2 is reduced in the diabetic animals in comparison to controls, while ACE is increased. In this study they also show that ACE and ACE2 are colocalized in the renal tubule.
Human data are just starting to accumulate. Wagner et al. reported that Ang II type 1 (AT$_1$) receptor expression was decreased by approximately 90% in patients with type 2 diabetes mellitus and diabetic nephropathy (12). It has been suggested that while the plasma renin activity may be low in diabetes mellitus, intrarenal levels of Ang II may well be elevated, which might downregulate AT$_1$ receptors (13). Konoshita et al. (14) observed increases in ACE mRNA in renal tissue from eight patients with type 2 diabetes mellitus and compared the findings to those from renal tissue in 66 nondiabetic subjects. These authors also observed that neither renin nor Ang II type 2 receptor (AT$_2$) mRNA differed between diabetic and nondiabetic subjects, while AT$_1$ and angiotensinogen mRNA was decreased.

The Konoshita et al. study (14) also reported observations on ACE2: It was no different in the kidneys of diabetic as compared with nondiabetic subjects. However, taken together, the data from human kidneys on ACE2 are limited. What about the ACE2 gene itself and diabetes in humans? Frojdo et al. (15) examined ACE2 polymorphisms in type 1 diabetes mellitus and found no association between polymorphisms and the risk of diabetes. However, the study did not exclude a weak association, and further studies would clearly be needed to assess that possibility.

The most important aspect of the Ye et al. report in this issue of JASN (11) is that the work assessed the effect of an ACE2 antagonist, MLN-4760, with or without an angiotensin receptor blocker (telmisartan). MLN-4760 increased urinary albumin excretion in diabetic animals, but not in db/m controls. ACE2 is not responsive to ACE inhibitors, although at least two ACE2 blockers do exist. ACE2 knockout animals have been developed. Over time, otherwise normal male knockout animals develop proteinuria, but females do not. So, it is not surprising that the normal animals in this study do not develop proteinuria when MLN-4760 is used. It would have been interesting to study male animals, given gender differences, particularly with ACE2.

Results in experimental models of diabetes differ from each other and from those in humans, an important issue for developing therapeutic strategies. What of ACE2 and development of therapies? In their article, Ye et al. suggest that ACE2 may regulate the levels of Ang II within the glomerulus by degrading it to Ang 1-7, a suggestion supported by the known actions of the enzyme (11). Ang 1-7 has recently been shown to inhibit Ang II–stimulated phosphorylation of MAP kinases in the proximal renal tubular cells, which is protective (16). Ang 1-7 also increases NO and prostacycline release and potentiates the effects of bradykinin. Such actions provide a rationale for embarking on strategies that might increase ACE2 in diabetes. Produced by ACE2, Ang 1-7 appears to have antiproliferative effects, and also has diuretic and natriuretic effects. It inhibits O$_2$ consumption as well. Thus, it might make sense to increase ACE2 and, thus, Ang 1-7 (5). Katovich and colleagues (17) have proposed gene therapy, showing its relevance by cloning ACE2 into a lentiviral vector in a sense direction to cause overexpression. Their studies suggest that this is potentially useful, as animals overexpressing ACE2 did not develop cardiac hypertrophy when Ang II was infused. Katovich et al. (17) also propose direct injection of the ACE2 gene. Such an experimental direction seems exciting, but the species variability of intrarenal ACE and ACE2 expression, as well as the present state of gene therapy strategies, would imply that it will take some time before the promise of ACE2 enhancement is clinically available.

References

See the related article, “Glomerular Localization and Expression of Angiotensin-Converting Enzyme 2 and Angiotensin-Converting Enzyme: Implications for Albuminuria in Diabetes,” on pages 3067–3075.