Endothelin Antagonists in Diabetic Nephropathy: Back to Basics

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The pivotal discovery of endothelin (ET) by Yanagisawa and colleagues1 in 1988 generated wide interest in this peptide, as evidenced by the nearly 27,000 articles published to date that have examined its role in biology. ET is now recognized as essential to the function of various organs and metabolic processes.2 The ET family consists of three 21–amino acid peptides—ET-1 (ubiquitous and most biologically active), ET-2, and ET-3—that exert their actions via two receptor subtypes: ETₐ and ETₐ receptors.³ Activation of these receptors usually, but not always, incites opposing actions; an additional consideration is that the ETₐ receptor also acts as a clearance receptor.³ Consequently, the effects of ET can vary among different organs depending on the amount being formed and on the receptor subtypes present. For instance, in the cardiovascular system ET induces vasoconstriction and growth via ETₐ receptors and vasodilation and growth inhibition via ETₐ receptors.¹,³ The net effect results in an increase in systemic vascular resistance and BP. This potentially injurious effect is augmented by ET’s ability to stimulate growth factors and cytokines, which induce neutrophil adhesion, platelet aggregation, and formation of extracellular matrix protein.³ Together, these actions can precipitate a vicious cycle that accelerates hypertension and atherosclerosis-induced vascular disease.³

Despite its importance in the cardiovascular system, ET plays an even larger role in regulating renal function and injury. This is because the kidneys are exquisitely sensitive to ET-1 (up to 10-fold more than are other organs⁴) and because the components of the ET system are widely distributed throughout the kidney; ET-1 is present in the renal microvasculature, in all types of glomerular cells, and in the tubules (the renal medulla contains the highest ET-1 levels in the body⁵). Thus, it is no surprise that ET-1 has such a key role in regulating renal hemodynamics, salt and water homeostasis, and acid-base balance⁶ and in modulating cell proliferation, extracellular matrix accumulation, inflammation, and fibrosis.⁷ Consequently, any abnormality in the intrarenal ET system may result in renal dysfunction (e.g., salt sensitivity) and/or injury. Indeed, ET may participate in the progression of renal injury during obesity, hypertension, and diabetes.⁷ Because most of the deleterious effects of ET-1 appear to be mediated through the ETₐ receptors, this receptor has become an attractive therapeutic target in various forms of cardiovascular and renal diseases, such as diabetes.³

Diabetic nephropathy is an attractive target for ET-1 blockade because several lines of evidence implicate ET in this disease. First, the synthesis and/or effects of ET-1 are increased in response to hyperglycemia, hypertensive glomerular injury, and insulin,⁸ which results in increased renal expression and systemic circulatory levels of ET-1 in experimental and clinical diabetes.⁹,¹⁰ Second, abnormalities in the ET system are present in the renal areas targeted by diabetes, including the microvasculature, mesangial cells, and podocytes.¹¹ Third, overactivity of ET-1 promotes proliferation, inflammation, fibrosis, and ultimately glomerulosclerosis.⁹ Finally, several studies have shown that ET receptor antagonists ameliorate experimental diabetic nephropathy.⁵,¹²,¹³ It is within this context that two
papers in this issue of JASN are of special interest: an experimental study that elucidates the functional significance of the ET\(_A\) and ET\(_B\) receptors on podocytes in diabetic kidney injury and a complementary clinical study demonstrating the antiproteinuric effects of an ET antagonist in diabetic nephropathy.

In the experimental study, Lenoir et al.\(^{14}\) used a novel mutant mouse wherein podocyte-specific, double deletion of the ET\(_A\) and ET\(_B\) receptors was induced. They not only demonstrated that these mice were protected against diabetes-induced podocyte loss and the attendant glomerulosclerosis but also provide evidence that the ET\(_B\) receptor may play an important role as does the ET\(_A\) receptor; this finding challenges the widely held notion that the deleterious effects of ET in diabetes are due to activation of the ET\(_A\) receptor. Indeed, ET\(_B\) receptor activation increased intracellular calcium and triggered the NF-κB and β-catenin signaling pathways, analogous to activation of the ET\(_{A}\) receptor. The quantitative contribution of the ET\(_B\) receptor may be substantial, as suggested by the fact that it is upregulated to a larger extent than the ET\(_{A}\) receptors in the podocytes of diabetic mice. While such cosignaling of ET has been reported in other cells, this appears to be the first study that suggests an important role for it in mediating podocyte injury during diabetes. This study implies that dual blockade of the ET\(_A\) and ET\(_B\) receptors may be necessary to achieve maximal benefit in diabetic nephropathy. These findings are novel and very significant because they question the strategy of the clinical trials targeting the ET\(_A\) receptor to avoid the adverse effects attributed to ET\(_B\) receptor blockade. The importance of the studies of Lenoir et al. is that they delineate ET–1–driven pathways, centered on the podocyte, as central contributors to the evolution of diabetic nephropathy.

Such experimental studies, in conjunction with the recognition that the podocyte is the principal determinant of glomerular permselectivity, naturally stimulate interest in antagonism of ET as a therapeutic approach in reducing proteinuria and the progression of diabetic nephropathy. Indeed, prior studies found that ET antagonists reduce proteinuria in diabetic and nondiabetic CKD.\(^7\) These promising results led to the ASCEND (A Randomised, Double Blind, Placebo Controlled, Parallel Group Study to Assess the Effect of the Endothelin Receptor Antagonist Avosentan on Time to Doubling of Serum Creatinine, End Stage Renal Disease or Death in Patients With Type 2 Diabetes Mellitus and Diabetic Nephropathy) trial, which involved 1392 patients with type 2 diabetes and evaluated the effect of avosentan on progression of overt diabetic nephropathy.\(^{15}\) As was seen in smaller previous trials, avosentan reduced proteinuria (by almost 50%). However, this trial was terminated early because avosentan use was associated with a greater incidence of serious adverse cardiovascular events, particularly edema and heart failure.\(^{13,16}\)

These results mimic those in other cardiovascular illnesses in which adverse effects, predominantly fluid overload, limited the usefulness of the drug. In hindsight, the adverse effect profile of ET-1 antagonists should be of no surprise because of the complexity of the ET system. Indeed, this complexity is not only limited to the ubiquitous distribution of the system and its competing receptor subtypes; it also is related to the distinct dose-dependent effects of ET-1 and the strong modulatory effect that numerous factors (e.g., nitric oxide, cytokines, inflammation) exert on ET-1 activity. Moreover, certain patient populations may be more prone to the adverse effects of ET blockade than others.\(^{16}\)

In the related clinical study, de Zeeuw et al.\(^{17}\) conducted a multicenter, multinational trial that examined the efficacy (reduction of albuminuria) and the adverse effect profile of atrasentan added to renin-angiotensin system inhibitor therapy. It is an extension of a previous dose-response study conducted by Kohan et al.\(^{13}\) in which addition of atrasentan to renin-angiotensin system inhibition decreased albuminuria without increasing edema. In addition to demonstrating the effectiveness of atrasentan in a larger patient population, the study by de Zeeuw and colleagues also addressed several of the mechanisms that probably contributed to the adverse effect profile of previous studies. First, they screened their patients carefully to avoid enrolling patients who already were fluid overloaded or prone to fluid overload. Second, they used a more selective ET\(_A\) antagonist, atrasentan, with the intent of preserving the beneficial actions of the ET\(_B\) receptor on salt and water balance. Third, they used a lower dose of atrasentan, one that preserved its albuminuria-lowering effect while having a favorable adverse effect profile. This study was a success in that the authors identified a dose of atrasentan with a favorable risk/benefit ratio in the patient population studied, therefore providing a dose that will be used in future studies. While this study is a positive step forward, it is just one of several steps that need to be taken, particularly in light of the results of Lenoir and colleagues’ study, suggesting that blockade of the ET\(_B\) receptor may also be required to achieve maximal efficacy of ET blockade.

There is a trend in the United States to encourage rapid progression of basic scientific discoveries into clinically relevant strategies, a concept referred to as translational research.\(^{18}\) It is important to remember that successful translational research has its foundation on basic research, which provides not only the fundamental information necessary to commence the translation but also the knowledge needed to develop strategies to overcome therapeutic obstacles (such as the adverse effects elicited by the ET blockers). As studies that center on the functional significance of the ET system in diabetic nephropathy, these two papers in this issue of JASN, considered together, represent an outstanding example of translational extension of basic research into novel therapies for a major form of CKD. Previous experimental studies demonstrating the significance of ET in the pathogenesis of diabetic nephropathy were the foundation of the current clinical trial by de Zeeuw et al. It is commendable that the authors successfully addressed some of the potential sources of the adverse effects so that the therapy may be better tolerated. As a result, a clinical trial that examines the efficacy of atrasentan on preventing progression of diabetic nephropathy is now
underway (Study of Diabetic Nephropathy with Atrasentan [SONAR]). However, for ET blockers to realize their potential, further information must be obtained regarding the basic mechanisms of how and when they work. An incremental advance is the study by Lenoir et al., which demonstrates that the ET₃ receptor may need to be targeted as well to maximize renal protection in diabetic nephropathy. However, because of the adverse effect profile related to ET₃ blockade (particularly the sodium retention), basic research elucidating the mechanisms involved in ET–blockade-induced adverse effects is needed so that better strategies can be devised to correct or override them, and as a result provide a more favorable risk/benefit profile.

In summary, there is a critical need to develop additional therapies to improve the treatment of diabetic nephropathy; ET antagonists hold considerable promise. However, for this promise to be fulfilled, researchers must continue to identify the basic mechanisms by which ET-1 contributes to diabetic nephropathy, as well as the mechanisms of adverse effects induced by ET antagonists. Despite the vast volume of basic research on the ET system, the clinical trials have just emphasized the need to return to the bench to further our understanding of its fundamental mechanisms. This is important for the development of maximally effective therapeutic strategies with minimal adverse effects.

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REFERENCES


See related articles, “Direct Action of Endothelin-1 on Podocytes Promotes Diabetic Glomerulosclerosis,” and “The Endothelin Antagonist Atrasentan Lowers Residual Albuminuria in Patients with Type 2 Diabetic Nephropathy,” on pages 1050–1062 and 1073–1083, respectively.

HDL in CKD: How Good Is the “Good Cholesterol?”

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