Endothelin and endothelin antagonists in chronic kidney disease

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The incidence and prevalence of chronic kidney disease (CKD), with diabetes and hypertension accounting for the majority of cases, is on the rise, with up to 160 million individuals worldwide predicted to be affected by 2020. Given that current treatment options, primarily targeted at the renin-angiotensin system, only modestly slow down progression to end-stage renal disease, the urgent need for additional effective therapeutics is evident. Endothelin-1 (ET-1), largely through activation of endothelin A receptors, has been strongly implicated in renal cell injury, proteinuria, inflammation, and fibrosis leading to CKD. Endothelin receptor antagonists (ERAs) have been demonstrated to ameliorate or even reverse renal injury and/or fibrosis in experimental models of CKD, whereas clinical trials indicate a substantial antiproteinuric effect of ERAs in diabetic and nondiabetic CKD patients even on top of maximal renin-angiotensin system blockade. This review summarizes the role of ET in CKD pathogenesis and discusses the potential therapeutic benefit of targeting the ET system in CKD, with attention to the risks and benefits of such an approach.

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CHRONIC KIDNEY DISEASE: A GROWING NEED FOR ADDITIONAL THERAPIES

The global community is witnessing steadily increasing numbers of patients with chronic kidney disease (CKD), with diabetes and hypertension accounting for the majority of cases.[1,2] Up to 11% of the general population of the United States, Australia, Japan, and Europe is currently affected, and numbers continue to increase in India, China, and Southeast Asia.[3,4] In view of the continuing obesity/diabetes pandemic and shifts toward older populations around the world, and given that current therapies only partially slow down progression to end-stage renal disease, the urgent need for additional, effective therapeutic agents lacking off-target effects is apparent.[1,4] Although multiple potential drug targets are in the development pipeline, the endothelin (ET) system has received particularly high attention. As will be described, the renal ET system is activated in virtually all causes of CKD. In addition, blocking specific ET system pathways holds the promise to be of significant therapeutic benefit in slowing CKD progression. However, owing to the potential for side effects, ET system blockers must be used carefully and judiciously. Herein, we briefly describe the physiology and pathophysiology of the renal ET system, followed by review of clinical experience with ET blockers, their potential side effects, and finally discuss the future therapeutic potential of, and approach to, targeting the ET system in CKD.

THE ET SYSTEM IN RENAL PHYSIOLOGY

The ET family comprises three 21-amino-acid peptides (ET-1, ET-2, and ET-3), of which ET-1 is the most biologically relevant to kidney function in health and disease. Although ET-1 was originally described as an endothelium-derived vasoconstrictor,[5] it is now evident that the peptide is produced by and acts upon virtually every cell type in the body.[6] ETs bind to two receptor isoforms: ET_A and ET_B.[6,7] In general, under healthy conditions, binding to ET_A promotes vasoconstriction, cell proliferation, and matrix accumulation; ET_B activation is vasodilatory, antiproliferative, and antifibrotic; however, under some pathological conditions, ET_B can promote tissue injury and scarring (please see following sections). These effects of

ET-1, whether in health or disease, are primarily exerted through local binding, i.e., the peptide acts in an autocrine and/or paracrine manner.

Endogenous renal ET is an important regulator of renal sodium and water excretion.[7] Volume loading increases nephron ET-1 production, which, largely through autocrine activation of thick ascending limb and collecting duct ET_B (leading to production of nitric oxide, as well as other signaling molecules), inhibits sodium and water reabsorption.[7] Nephron, and particularly collecting duct, ET_A also appears to exert a natriuretic effect;[8,9] however, the mechanisms by which this occurs remain unclear. Blockade of ET receptors is associated with fluid retention and, as will be described, this side effect has had significant clinical impact. Endothelin receptor antagonists (ERAs) target ET_A alone or both ET_A and ET_B (never just ET_B); all clinically used ERAs cause fluid retention. On the basis of the predicted ET-1 actions in the kidney, such fluid retention is perhaps not surprising. In support of a renal cause of fluid retention, recent studies in mice using two different relatively ET_A-selective antagonists (atrasentan and ambrisentan) showed that the fluid retention was prevented by either nephron or collecting duct–specific deletion of ET_A receptors.[8]

Renal ET also modulates other aspects of renal physiology, including total and regional blood flow, mesangial contraction, podocyte function, and acid/base handling. ET involvement in renal acid secretion may take on particular relevance in CKD. Acid loading increases renal ET-1 production, which, in turn, stimulates proximal and distal nephron proton secretion; blockade of the ET system impairs normal renal acid excretion.[10] As will be discussed, acidemia that occurs in the setting of CKD promotes renal ET-1 production that, through promotion of profibrotic pathways, may contribute to progressive deterioration of renal function.

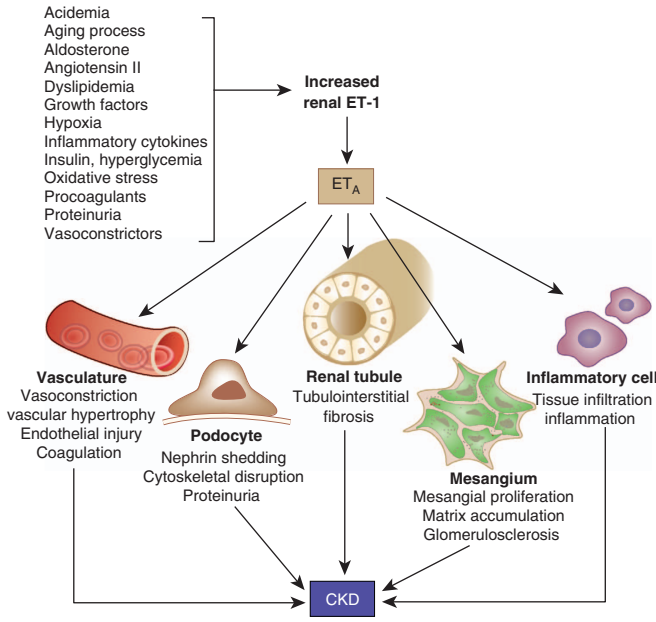

Figure 1 | Pathophysiological role of endothelin in chronic kidney disease (CKD) development. Intrinsic (aging), physicochemical (acidemia, hypoxia), biochemical (cytokines, oxidative stress, growth factors, and procoagulants), metabolic (insulin, hyperglycemia, and dyslipidemia), vasoactive (angiotensin II, aldosterone, and vasoconstrictors), and pathological factors (proteinuria) enhance renal endothelin-1 (ET-1) production. CKD development is associated with increased formation of renal ET-1, which—primarily via ET_A receptors—promotes renal injury and fibrosis through modulation of multiple renal cell types.

THE ET SYSTEM IN RENAL PATHOPHYSIOLOGY

ET has an important role in the development of proteinuria, fibrosis, and CKD progression.[6] ET-1 promotes cell proliferation, hypertrophy, inflammation, and extracellular matrix accumulation, all of which are important factors in the progression of CKD.[11,12] Renal ET-1 production increases in conditions associated with renal disease progression, such as diabetes, insulin resistance, obesity, immune system activation, dyslipidemia, reactive oxygen species formation, nitric oxide deficiency, and others (reviewed in Barton,[11] Figure 1). Infusion of nonpressor doses of ET-1 increases renal cortical inflammation (ICAM-1, MCP-1, and macrophages),[13] as well as podocyte effacement and urinary albumin excretion,[14] effects that are largely prevented by concomitant treatment with an ET_A antagonist.[13,14] ET-1 also increases the formation of other vasoconstrictors and growth factors (such as angiotensin II).[15] In turn, angiotensin II activates renal ET-1 formation,[16] thereby creating a positive feedback loop. Of note, ET-1 also appears to be involved in the priming effect of acute ischemic renal injury on future CKD development, and this effect can be largely prevented by blocking ET_A.[17]

One aspect of ET activity in renal pathophysiology deserving of particular mention is podocyte involvement. Podocyte injury is a hallmark of proteinuric renal diseases and precedes the development of glomerulosclerosis.[18,19] Podocytes and neighboring cells synthesize ET-1, and podocytes express both ET_A and ET_B.[18] In podocytes from humans and experimental animals, ET_A has been primarily implicated in mediating cellular injury,[18] although preliminary data from the Tharaux laboratory suggest that, at least in mice, activation of podocyte ET_B might also cause podocyte dysfunction.[20] The mechanisms by which ET-1 contributes to podocyte injury are not fully understood and are likely to be multifactorial. Exposure to ET-1 *in vitro* disrupts the podocyte actin cytoskeleton,[21,22] whereas treatment with ERAs prevents disruption of the podocyte actin cytoskeleton in experimental focal segmental glomerulosclerosis (FSGS).[18] Interestingly, exposure of podocytes to protein *in vitro* (mimicking proteinuria *in vivo*) induces the synthesis of ET-1 and reduces glomerular permselectivity, an effect sensitive to ET_A blockade.[22,23] Further, exogenous ET-1 chronically increases glomerular permeability via ET_A-mediated mechanisms.[14,24]