Role of endothelin in chronic renal failure—developments in renal involvement

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Endothelin (ET)-1 is a potent vasoconstrictor with profibrotic and proinflammatory effects. Increasing evidence suggests that ET-1 and its cognate receptors are involved in a variety of progressive renal disorders, including diabetes, hypertension and glomerulonephritis. Several laboratory studies have demonstrated elevated expression of ET-1, which colocalizes with glomerular and tubulointerstitial injury, in addition to enhanced urinary excretion. Moreover, ET-1 expression correlates with disease severity and renal function. With the availability of ET receptor antagonists, a pathogenetic role has been further corroborated in animal models, demonstrating both structural and functional improvement. Thus, antagonizing the ET system may be useful in major renal pathologies associated with glomerular and tubulointerstitial damage.

Introduction

Endothelin (ET) is a potent vasoconstrictor peptide with profibrotic and pro-inflammatory potential that has been initially discovered in vascular endothelial cells [1]. During the recent years, it has become increasingly clear that a broad spectrum of cells has the ability to produce ET-1 under physiological conditions, and, more importantly, during the course of chronic progressive disorders.

ET-1 is intimately involved in normal renal function, modulating glomerular filtration rate (GFR), solute and water reabsorption along the nephron, and renal acid excretion. Following the discovery of the ET peptides by Yanagisawa et al. [1], however, substantial evidence has accumulated indicating that the ET system is implicated in several forms of chronic renal failure.

Renal glomerular, tubular and interstitial cells have not only the ability to respond to circulating ET-1 via binding to ET_A and ET_B receptors, but also to produce ET-1 in an autocrine/paracrine manner. During the course of chronic renal diseases, the intrarenal synthesis of ET-1 is remarkably up-regulated along with a modulation of ET receptor subtype expression, particularly at those sites affected by the pathological process. The present minireview will summarize the most impressive findings pointing to a pathogenetic role of the ET system in chronic fibrotic glomerular and tubulointerstitial disorders.

Role of ET system in chronic renal failure

Direct evidence for a causal role of ET-1 in renal fibrosis has been provided by Hocher et al. [2]. Transgenic mice overexpressing human ET-1 in the kidney time-dependently develop glomerulosclerosis, tubulointerstitial fibrosis and renal cysts, which occurs in parallel with a reduction in GFR [2]. These observations strengthen the concept that increased intrarenal ET-1 production is sufficient to cause morphological and functional alterations characteristic for chronic renal failure, rather than being an epiphenomenon during the course of chronic renal disorders. However, this raises the question on the mechanism of increased intrarenal ET-1 production and the mode of action in chronic renal diseases.

Hypertension, diabetes and glomerulonephritis represent the major human pathologies associated with chronic glomerular and tubulointerstitial injury. A common feature in chronic renal disease, either related to immune or non-immune causes, is the progressive loss of functional nephrons. Consequently, those nephrons with initial minor functional impairment undergo hypertrophy, with an increase in single nephron GFR, aiming to maintain total GFR [3]. This process, however, at least in the long-term, initiates a vicious circle, leading to progressive glomerular injury with subsequent glomerular barrier dysfunction [4].

Most likely, proteinuria is causally involved in progressive structural and functional renal deterioration, since the degree of proteinuria directly reflects the severity of renal injury, and therapeutic manoeuvres that reduce proteinuria also slow the underlying disease progress [5]. Elegant work by Benigni and coworkers [6] provided a mechanistic link between glomerular barrier dysfunction and proteinuria, increased intrarenal production of ET-1 and progressive renal failure. In rats, renal mass reduction (5/6 nephrectomy; simulating the loss of functional nephrons) caused a time-dependent increase in proteinuria, which paralleled the up-regulation of intrarenal ET-1 mRNA expression [7]. Accordingly, *in vitro* exposure of proximal tubular epithelial cells to high-molecular-weight proteins such as albumin, IgG and transferrin elicits a dose-dependent production of ET-1, which is primarily released abuminally into the interstitial compartment, while only a minor portion is secreted luminally and thus appears in the urine [6]. In agreement, systemic levels of ET-1 are elevated in chronic renal failure, and urinary ET-1 excretion is about five times increased compared with healthy subjects [8].

Role of ET system in glomerular fibrosis

Several conditions known to cause progressive glomerular injury have the ability to stimulate intraglomerular ET-1 expression. In streptozotocin-diabetic rats, glomerular ET-1 expression and urinary ET-1 excretion increase markedly [9]. Studies on primary cultures of rat mesangial cells have demonstrated that elevated glucose levels per se are sufficient to stimulate ET-1 promoter activity and ET-1 expression [9]. ET-1 produced by glomerular cells may exert biological effect in an autocrine/paracrine manner on glomerular cells itself, or, via peritubular capillaries,
ET-1 in tubulointerstitial fibrosis

The second major histomorphological alteration in progressive renal failure is tubulointerstitial inflammation and fibrosis. Increased tubulointerstitial ET-1 abundance may result from protein challenge of proximal tubular epithelial cells (mentioned earlier) and from ET-1 produced within glomeruli, reaching the tubulointerstitial compartment via peritubular capillaries originating from efferent arterioles. Locally released ET-1 may trigger renal injury by two mechanisms. First, ET-1 may cause constriction of peritubular capillaries with subsequent hypoxic injury of neighbouring proximal tubules based on their high metabolic demands. Hypoxia, in turn, which is a major stimulus for ET-1 expression, may trigger ET-1 production in tubular epithelial cells, thereby potentially initiating a vicious circle. Secondly, ET-1 is not only a potent vasoconstrictor, but also promotes accumulation of inflammatory cells and extracellular matrix production. Accordingly, activation of nuclear factor (NF)-κB (which drives the expression of many pro-inflammatory cytokines) is prominent in proximal tubules and infiltrating mononuclear cells in rats with intense proteinuria, whereas ET antagonism reduces NF-κB activation, interstitial infiltration and renal lesions [17].

Conclusions

The following observations support a pathogenetic role of the ET system in conditions associated with progressive glomerular and tubulointerstitial inflammation and fibrosis, including diabetes, hypertension and glomerulonephritis:

- Persistent proteinuria as present during the course of chronic renal disorders stimulates ET-1 production.
- ET-1, via binding to ETA and ETB receptors, mediates extracellular matrix production, inflammation and vasoconstriction.
- ET receptor antagonism ameliorates renal pathology and improves renal function in animal models.

**References**


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<td>- The initiation and perpetuation of progressive renal pathologies correlate with the expression and urinary excretion of ET-1.</td>
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<td>- Activation of the ET system co-localizes to structural lesions.</td>
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C.R. received speaker’s honorarium for participation at Actelion Winter School 2006.