Interstitial Inflammation and Fibrosis

Tubulointerstitial disease mediators of injury: the role of endothelin

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Progression to end-stage renal failure is the final common pathway of several chronic nephropathies independently from their aetiology. Brenner et al. [1] first offered the most consistent unifying hypothesis on the progressive nature of renal disease, suggesting that the surviving nephrons initially spared by the disease activate common haemodynamic responses which, while serving to maintain glomerular filtration, cause structural injury in a self-perpetuating cycle [1]. More recently, studies have established that an excessive and sustained protein traffic through the nephron, as a consequence of high glomerular capillary pressure, invariably is associated with the progress of the disease and exerts intrinsic renal toxicity per se [2]. The proteins filtered in excessive amounts accumulate in the lumen of the proximal tubule and are actively reabsorbed by the tubular epithelium, causing an intracellular congestion that, in the long term, promotes tubulointerstitial injury and renal scarring. Excessive protein reabsorption would induce functional alterations of tubular cells that overexpress inflammatory and vasoactive molecules mainly secreted towards the interstitium where they trigger an interstitial inflammatory reaction, fibroblast proliferation and extracellular matrix deposition, key features of renal scarring. Overload of proximal tubular cells in culture with excess proteins induces a dose-dependent increase in the synthesis and release of endothelin-1 (ET-1) [3], a peptide with vasoconstrictor and proliferation properties, which, by virtue of its chemotactic activity, attracts blood monocytes and stimulates them to produce proinflammatory cytokines, which would further amplify the interstitial inflammatory reaction.

Increased renal gene expression and synthesis of ET-1 have been reported in proteinuric progressive nephropathies from either immune or non-immune origin (Table 1). The remnant kidney model in the rat is characterized by a time-dependent increase in renal ET-1 gene expression, paralleled by an increase in urinary excretion of the peptide, that probably reflects its renal synthesis. The time course of endothelin receptor expression revealed a selective increase in ET\textsubscript{B} receptor gene expression in remnant kidney rats, possibly as a consequence of compensatory renal hypertrophy, as recently demonstrated in ET\textsubscript{B} knockout mice [4]. Changes in renal ET-1 expression/synthesis correlate with progressive renal damage in this model [5–7]. Increased renal synthesis of ET-1 was also found in rats with passive Heymann nephritis (PHN), an immune model of glomerular disease resembling human membranous nephropathy [8,9]. Other studies have found an up-regulation of renal ET-1 and ET\textsubscript{A} receptor gene expression in NZB/WF1 mice that have an immunological disease reminiscent of human lupus [10]. Glomerular ET-1 and ET\textsubscript{B} receptor mRNAs were higher than normal within few days after puromycin aminonucleoside injection and normalized when rats were no longer nephrotic [11]. Also in experimental diabetes, mRNA for ET-1 is overexpressed in the kidney in the face of unchanged ET\textsubscript{A} and ET\textsubscript{B} receptors [12].

The most elegant and direct evidence that ET-1 plays a role in progressive renal damage derives from studies using transgenic animals. Mice overexpressing the human ET-1 promoter generate more ET-1 in their kidney and develop renal lesions despite no increase in systemic blood pressure [13]. Furthermore, rats transgenic for the human ET-2 gene are normotensive and develop renal lesions reminiscent of those seen in rats with remnant kidney [14]. Several lines of evidence using ET receptor antagonists definitely support the possible role of ET-1 in renal diseases and provide important indications for future clinical use of these compounds to slow or even halt disease progression. Thus, in the rat remnant kidney model, a specific antagonist for the ET\textsubscript{A} receptor [15] ameliorated renal function and protected against glomerular and tubulo-interstitial structural injury. Similar results have been achieved recently using an ET\textsubscript{A} and a non-selective ET\textsubscript{A}/ET\textsubscript{B} [16] receptor antagonist. Furthermore, an orally active compound with antagonizing properties for ET\textsubscript{A} and ET\textsubscript{B} receptors [17] even prolonged survival. Interestingly, endothelin receptor antagonists, that invariably reduce renal damage, did not normalize proteinuria consistently, confirming the possibility that excessive ET-1 does not cause, but is rather the consequence of, increased glomerular protein traffic [2]. The renoprotective effect of ET\textsubscript{A} receptor antagonists was also evident in mice with experimental lupus
nephritis [18]. The same molecule was effective in preventing the development of renal lesions and attenuating the increase in serum creatinine in rats with streptozotocin-induced experimental diabetes treated at the moment of induction of the disease [19]. More recently, data became available to indicate that an unselective ET<sub>A</sub>/ET<sub>B</sub> receptor antagonist, when chronically administered to diabetic animals with overt proteinuria, was as effective as an angiotensin-converting enzyme inhibitor (ACEI) on blood pressure and protein excretion [20].

Pharmacological tools, which effectively reduce proteinuria, such as the ACEIs, also limit renal damage and prevent renal function deterioration. These effects invariably were associated with reduction of the exaggerated renal synthesis of ET-1. A recent study [21] has indicated that in a model of accelerated PHN, that does not completely respond to ACEIs, the combination of ACEI with a selective antagonist for the ET<sub>A</sub> receptor has a superior renoprotective effect than single therapy alone. Altogether, the above evidence indicates that ET-1 is a major mediator of renal damage whose synthesis is induced by excessive protein reabsorption in the tubular cells. Concomitant administration of drugs that reduce protein traffic and block endothelin receptors would represent the basis for future treatment of progressive nephropathies.

Evidence for a potential role of ET-1 is also available for patients with chronic progressive nephropathies, but data are based solely on plasma and urine immunoreactive ET-1 measurements (Table 1) or expression of endothelin/endothelin receptor genes in the kidney. Plasma concentrations of ET-1 in patients with chronic renal failure are 1- to 2-fold greater than normal [23]. Increased circulating ET-1 concentration in these subjects may reflect impairment of clearance. However, the fact that urinary excretion of ET-1 is also increased in patients with chronic nephropathies [22] suggests that renal generation of ET-1 in these diseases is increased. Moreover, administration of an ET<sub>A</sub>/ET<sub>B</sub> receptor antagonist to patients with chronic renal failure reduced blood pressure and renal vascular resistance [24]. A very recent study has shown that patients with chronic glomerulopathy whose urinary protein excretion was >2 g, had an increased expression of ET-1 and ET<sub>B</sub> receptor in their kidney, as previously observed in rats with progressive renal disease [25].

Pre-clinical studies consistently have demonstrated a role for ET-1 in renal disease progression and a considerable renoprotection of endothelin receptor antagonists. Clinical studies are now mandatory to assess the applicability of such animal results to human.

### Table 1. Increased renal endothelin expression/synthesis in chronic renal diseases

<table>
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References


