Modulation of the renin–angiotensin system in proteinuric renal disease: are there added benefits?

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Introduction

Most forms of progressive renal disease follow a final common pathway resulting in tubular atrophy, interstitial scarring and an interstitial inflammatory cell infiltrate [1]. The onset and degree of proteinuria is associated with a poor prognosis and has recently led to an increased interest in characterizing the pathogenic role proteinuria plays in the progression of renal damage. Evidence is accumulating that the filtration of excessive proteins by the glomerulus together with their subsequent reabsorption exerts a toxic effect on the proximal tubular epithelial cell in the manner of a signalling molecule [2,3]. This protracted over-reabsorption of protein results in the activation of pro-inflammatory pathways, which trigger inflammation in the interstitium. It is the severity of the resultant interstitial fibrosis that correlates most closely with the degree of renal impairment and subsequent prognosis. Studies performed using angiotensin converting enzyme (ACE) inhibitors have demonstrated the beneficial effect of modulating the renin–angiotensin system (RAS) in proteinuric renal disease [4–6]. These effects are secondary to a reduction in angiotensin II (AII) formation and are in part independent of the drug’s ability to lower systemic blood pressure. Angiotensin II plays a central role in the pathogenesis of progressive renal disease through the stimulation of cell growth, extracellular matrix deposition, and the synthesis of chemotactic factors [7].

We and others have proposed that the presence of excessive protein in tubular fluid of proteinuric renal disease enhances the pro-inflammatory effects of angiotensin II and contributes to the development of interstitial fibrosis. Therapeutic intervention using ACE inhibitors or the newly introduced angiotensin II receptor antagonists (AIIRAs) would thus have the added benefit of being able to modulate this interaction at the molecular level, in a manner that is again independent of the drug’s haemodynamic effects.

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The role of the RAS in the development of tubulointerstitial disease

The role of the RAS in the development of tubulointerstitial disease has been demonstrated in a number of clinical studies in which ACE inhibitors have successfully ameliorated the course of both diabetic and non-diabetic renal disease progression [4–6]. It has been suggested that ACE inhibitors possess a specific renoprotective action through an ability to reduce both systemic and glomerular hypertension [8]. Further work has shown that AII is capable of mediating a number of pro-inflammatory effects in the kidney that are independent of its haemodynamic actions. The kidney has its own independent RAS with all the necessary components for the generation of AII. Indeed, the proximal tubular luminal fluid concentrations of AII have been measured and found to be ~1000-fold greater than the circulating plasma levels of AII [9].

Angiotensin II mediates its effects primarily through two types of AII receptors: the AII type 1 (AT1) receptor and the AII type 2 (AT2) receptor [10]. Both receptor subtypes are expressed in the kidney and in particular on the proximal tubular epithelial cell, with the majority of the effects of AII mediated by the AT1 receptor. Signalling through the AT1 receptor stimulates a number of responses that have been implicated in the development of interstitial fibrosis. These responses include stimulation of tubular epithelial cell hypertrophy, synthesis of extracellular matrix proteins and the generation of oxygen free radicals [11]. AT1 receptor blockade reduces extracellular matrix deposition in the rat kidney following subtotal nephrectomy, confirming a role for AII acting through the AT1 receptor in this model [12]. Angiotensin II is also capable of modulating immune responses in the kidney through the induction of pro-inflammatory chemokines such as MCP-1 and RANTES [7]. On the other hand, stimulation of the AT2 receptor acts to counterbalance the effects of the AT1 receptor through its antiproliferative effect and participation in cell apoptosis. It appears that a degree of communication exists between both receptor subtypes to maintain a balance. At the molecular level it has been shown that AII mediates its inflammatory promoting effects through the activation of nuclear factor-κB (NF-κB) in vascular smooth muscle and mesangial cells [13,14]. NF-κB is a family of transcription factors that bind to DNA motifs present in the promoter sequences of various genes, particularly those associated with inflammatory or immune responses. Expression of the AII-induced genes MCP-1, RANTES and angiotensinogen is regulated by NF-κB [14–16]. It is notable that with respect to angiotensinogen there is the potential for an autocrine reinforcing loop to occur, with its upregulation by AII leading to further AII production and perpetuation of an inflammatory response. Currently, there is little published data on how AII could modulate pro-inflammatory pathways through NF-κB activation specifically in the proximal tubular epithelial cell. Angiotensin II activates NF-κB through both AT1 and AT2 receptors, and further work is necessary to identify which receptor subtype is responsible for mediating the stimulatory effects of AII in the proximal tubular epithelial cell.

The role of proteinuria in the development of tubulointerstitial disease

The development of proteinuria in most forms of chronic renal failure indicates a poor prognosis, with amelioration of the rate of decline in renal function by ACE inhibitors occurring in association with a reduction in proteinuria [4–6]. This not only provides an important link between the modulation of the RAS and proteinuria, but also strengthens the argument that proteinuria acts in a dynamic way to mediate the progression of renal failure, rather than simply being a marker of glomerular dysfunction. The exact mechanisms through which proteinuria induces interstitial fibrosis remain incompletely characterized. We and others have proposed that in proteinuric renal disease, proximal tubular epithelial cells are exposed to excessive and prolonged traffic of proteins, in particular albumin [2,3]. The resultant tubular cell protein overload upregulates pro-inflammatory pathways, which contribute to the development of interstitial inflammation and fibrosis. A number of experimental studies have shown that the exposure of proximal tubular epithelial cells in culture to protein stimulates the production of extracellular matrix proteins such as fibronectin, and the profibrotic chemokines MCP-1 and RANTES [17,18], in addition to activating mitogenic pathways [19]. These results indicate that protein may be able to exert effects on the proximal tubular epithelial cell in the manner of a pro-inflammatory signalling molecule. Immunohistochemistry performed on renal biopsy specimens from patients with severe proteinuria and progressive idiopathic membranous nephropathy has demonstrated overexpression of the chemokines MCP-1, RANTES and osteopontin in tubular epithelial cells [20].

It has been suggested that proteinuria could directly result in the activation of the RAS in the kidney. As already indicated, both AT1 and AT2 receptors are present on proximal tubular epithelial cells, and all of the necessary components of the RAS are present at the cellular level to generate AII. This theory is supported by data from the protein overload model, which has demonstrated increased ACE activity in the proximal tubules of rats with intense proteinuria [21]. Evidence exists that proteinuria may act at the molecular level to upregulate the activation of NF-κB [22], and therefore shares a common pathway with AII for the mediation of its pro-inflammatory actions. Increasing concentrations of albumin result in a dose-dependent increase in NF-κB activity in proximal tubular epithelial cells, whilst the use of an antioxidant...
inhibitor of NF-κB activation is able to prevent the generation of RANTES in response to protein [23]. Thus, changes in the tubular milieu, secondary to the development of proteinuria and in addition to upregulation of the local RAS, may act together to initiate interstitial inflammation and fibrosis.

The beneficial effects of AIIRAs vs ACE inhibition in proteinuric renal disease

It has been demonstrated that AIIRAs have comparable efficacy to that of ACE inhibitors in terms of their ability to reduce blood pressure and reduce proteinuria [24,25]. At the molecular level, both AIIRAs and ACE inhibitors have been shown to ameliorate the deposition of the extracellular matrix protein collagen IV in a model of interstitial fibrosis [26]. In the same model, however, only the ACE inhibitor was effective in reducing the inflammatory cell infiltrate. Long-term ACE inhibition results in suppression of AII to unmeasurable levels, whereas during angiotensin II receptor antagonism AII levels are high. The AIIRAs currently available are specific for the AT1 receptor and block its undesirable effects, leaving the AT2 receptor free. It has been argued that a further theoretical benefit of AT1 receptor blockade is the resulting stimulation of the AT2 receptor by the high circulating levels of AII. A number of studies have demonstrated the importance of the AT2 receptor in the pathogenesis of tubulointerstitial disease, with its absence or antagonism exacerbating the development of interstitial fibrosis [27,28].

Conclusion

Modulation of the RAS is able to slow the progression of renal disease through both haemodynamic and non-haemodynamic actions. It has been demonstrated that the beneficial effects of ACE inhibitors and AIIRAs on chronic renal failure occurs in association with a reduction in proteinuria, which is independent of a reduction in systemic blood pressure. It is therefore likely that proteinuria and angiotensin II act together to potentiate one another’s profibrogenic effects on the proximal tubular epithelial cell, and that the added benefits of modulating the RAS in proteinuric renal disease are related to the antagonism of these profibrogenic pathways. Further investigations are necessary to confirm this hypothesis and identify any potential advantage AIIRAs may have over ACE inhibitors in the treatment of proteinuric renal failure.

References


