Endothelin: The yin and yang of ischemic acute renal failure

In this month’s issue of *Kidney International* Forbes et al. study the long-term deleterious effects of single kidney ischemia and demonstrate the dual role played by the renal endothelin system in this destructive process [1]. Previously viewed as a transient and fully reversible form of renal injury, ischemia/reperfusion injury to the kidney has now been shown to lead to long-term damage of the kidney. The functional and morphologic characteristics of the damage are similar to other forms of experimental and human progressive renal failure. Thus, reduced glomerular filtration rate (GFR), loss of tubular epithelial cells, interstitial fibrosis, glomerulosclerosis, hypertension and mounting proteinuria are cardinal features of this form of renal insufficiency [2, 3]. These changes are associated with increased numbers of activated cells, myofibroblasts, monocytes and macrophages in the areas within and adjacent to the scarred interstitium. Of special interest is the fact that these changes occur in the absence of antecedent glomerular changes, indicating that the glomerular sclerosis is a product rather than a cause of these changes [3]. The progressive nature of this insult depends on the removal of at least the opposite kidney before ischemia is applied to the remaining kidney, since it does not occur in a single ischemic kidney when the contralateral normal kidney is in place [4]. Thus, it would appear that the development of renal failure occurs subsequent to ischemia only when the kidney is also undergoing a growth stimulus, but more on that later.

Forbes et al. show that blockade of the endothelin type A receptor (ET\textsubscript{A}) aborts these changes, indicating a role of endogenous ET in the progressive nature of solitary kidney ischemia. Surprisingly, however, while inhibition of both the ET\textsubscript{A} and ET\textsubscript{B} receptors ameliorates injury in the acute setting [5], inhibition of both of these receptors leads to more severe long-term damage. What could be the reason for this apparent paradox?

The kidney possesses all of the components of the endothelin system, where it is thought to act in an autocrine manner to affect renal function [6]. Endothelins 1 and 3 are produced normally in the endothelial and tubule compartments of the kidney, with the most production demonstrable in the vasa rectae and collecting ducts of the renal medulla [7]. Endothelin receptors A and B are found throughout the kidney, and probably overlap within the same site, though at different densities. In general, the A receptor is dominant in the vascular compartment, while the B receptor is more prominent in the tubule compartment. While also dependent on the specific cell type, it is generally observed that the A receptor is vasoconstrictive, while the B receptor vasodilates [6]. The latter effect has been attributed to the linkage of the ET\textsubscript{B} receptor to nitric oxide (NO) generation. Short-term infusion of endothelin vasoconstricts the afferent and efferent glomerular arterioles, and thereby raises intrarenal vascular resistance, reduces renal blood flow (RBF), and reduces GFR [8]. It also increases sodium chloride excretion most probably via basolateral membrane collecting duct B receptor mediated inhibition of the apical sodium channel [9]. After uninephrectomy, blockade of the ET\textsubscript{B} receptor aborts compensatory hypertrophy completely, demonstrating the potent growth potential of an activated ET system (abstract; Lui et al., *J Am Soc Nephrol* 10:496, 1999). Renal ischemia raises intrarenal ET-1 production [10], and thus renal ischemia applied to the kidney undergoing compensatory hypertrophy would most likely be a high renal endothelin production state. Anti-endothelin strategies have generally ameliorated the acute phases of the syndrome of ischemia/reperfusion renal failure, and the effects of ET\textsubscript{A} and ET\textsubscript{B} receptor blockade are indistinguishable up to two weeks after the ischemic episode. Indeed, it was surprising that the differences in outcome at six months would unmask a protective effect of the ET\textsubscript{B} system in ischemia.

Some hint of the resolution of this apparent paradox may be obtained from an analysis of the differences between the A and A/B receptor blocked groups. When both the A and B receptors are blocked, the ensuing renal failure and interstitial fibrosis are worse, the numbers of myofibroblasts, macrophages and monocytes are increased, and the cell cycle activity is increased above either the ET\textsubscript{A} blocked group or the ischemic controls. Inhibition of the ET\textsubscript{A} receptor reduced not only the functional and morphologic consequences of the emerging renal insufficiency but also reduced the numbers of cycling cells as well, indicating that cell cycle events are intimately related to the progressive nature of the insult. In renal ischemia/reperfusion injury, increased cell cycle activity occurs early in the first stages of reperfusion.
injury and, when unregulated produces greater cell death and worsens renal failure (abstract; Megyesi et al, J Am Soc Nephrol 11:461, 2000). When ischemia is applied to a solitary remaining kidney, it would appear that a second wave of increased DNA synthesis occurs much later (at least at 6 months in these studies), which appears to be mediated by the ET_A receptor. This later phase of increased cell cycle activity is pro-fibrotic and pro-inflammatory, and ultimately damaging. Also, as in the acute situation, when the tonic influence of an inherent anti-cell cycle effect is removed, in these studies by blockade of the ET_B receptor, cell cycle activity increases and results in greater damage. Thus, the role of endothelin at this later time point is a dual one. It promotes entry into the growth cycle of a variety of cells, including those within the tubule epithelium and interstitium, but also inhibits and modulates these stimuli to prevent some of the more deleterious aspects of cell activation, such as fibroblast activation and matrix production. Hence, endothelin is a growth factor and cytokine that promotes growth (abstract; Lui et al, ibid), enhances neutrophil-endothelial interactions [11], stimulates chemokine and cytokine synthesis [12], elevates NO synthesis [13], and is crucial developmentally [6]. Consistent with this view of the deleterious effects of unregulated endothelin stimulation is the observation that overexpression of endothelin in transgenic mice causes glomerulosclerosis and renal interstitial fibrosis [14]. In all of these aspects endothelin resembles angiotensin.

There is much to think about in these studies. Chief among them is whether these effects are due solely to the absence of an anti-fibrotic, anti-inflammatory, and anti-growth effect of the ET_B receptor alone, or to unopposed ET_A receptor activity as a consequence of the relative insensitivity of the ET_B receptor to this particular inhibitor. How many other states of high renal endothelin activity exist in which the progressive nature of the disease could be linked to the endothelin system? High circulating levels of endothelin have been documented in hemodialysis patients [1]. We should be quite concerned about any approach that focuses exclusively on blocking both the ET_A and ET_B receptors when the likelihood of elevated renal content of endothelin is high and the setting of renal transplant immediately comes to mind. The experience with solitary kidney ischemia demands that observations of any intervention on this level would require long-term follow-up and not be restricted to the early post-transplant period. Without a better understanding of ET_A and ET_B signaling events, the cells participating in ET mediated responses, and the interactions with ET receptor signaling and the cell cycle apparatus, combined with receptor blockade in this and other high endothelin states may be very detrimental to long-term survival.

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References