Life and Death of Podocytes: Not Only a Matter of Vascular Endothelial Growth Factor

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Renovascular disease (RVD) comprises a variety of conditions that alter the arterial supply of the kidney, inducing hypertension and affecting renal function, ultimately leading to chronic kidney disease. Although renal artery interventions are frequent therapeutic strategies for treating RVD, many patients derive little net benefit from them. This creates an urgent need for the identification of disease mediators that could be targeted to prevent irreversible injury in the post-stenotic kidney or other complications.

Soon after its discovery, endothelin-1 (ET-1) was identified as a key factor in controlling kidney function and promoting renal disease progression [1], due to its vasoconstrictive action and mitogenic property. More recently, the role of ET-1 in fostering renal injury in chronic RVD was put forward, with a particular focus on the roles of ET receptors, ET-1 type A (ET\textsubscript{A}) and ET-1 type B (ET\textsubscript{B}) [2, 3]. Results from these studies documented the disparate effects of the selective antagonism of ET\textsubscript{A} receptor compared to dual ET\textsubscript{A}/ET\textsubscript{B} [3] or ET\textsubscript{B} receptor [2] blockade in a porcine model of chronic RVD. While ET\textsubscript{A} receptor antagonist improved hypertension, microvascular rarefaction and renal injury, dual ET\textsubscript{A}/ET\textsubscript{B} blunted the therapeutic effects, and single ET\textsubscript{B} receptor inhibition was ineffective.

In the current issue of the American Journal of Nephrology, Harvey et al. further investigated the involvement of the ET-1 pathway in chronic RVD, examining the effects of the ET\textsubscript{A} and ET\textsubscript{B} receptor antagonism on podocyte integrity and survival in the ischemic kidney [4]. Podocytes are highly specialized epithelial cells constituting the outer layer of the glomerular filtration barrier, and their dysfunction and loss are hallmarks of proteinuric renal disease [5]. Notably, podocytes possess a fully functional ET system, and evidence has highlighted the role of ET-1 in promoting structural and functional alteration of these cells in renal disease [5]. Mindful of the previously reported in vivo effects of ET-1 blockade, in the present work, the authors exploited a hypoxic in vitro approach that offered the opportunity to dissect the mechanisms underlying podocyte injury and recovery by mimicking the renal environment of chronic RVD. They analysed human podocytes that were exposed to chronic hypoxia and treated with either an ET\textsubscript{A} or ET\textsubscript{B} receptor antagonist. Hypoxia decreased the podocyte count, while it increased the number of cells displaying morphological changes suggestive of apoptosis, such as nuclear condensation and fragmentation. These effects paralleled the decreased expression of vascular endothelial growth factor (VEGF) and slit diaphragm-associated proteins podocin and nephrin. Furthermore, hypoxic podocytes displayed increased expression of the anti-VEGF soluble receptor s-Flt 1 and of pro-apoptotic mediators, including BAX, p53 and SMAC. Treatment with ET\textsubscript{A} receptor antagonist
significantly improved podocyte survival, preserved VEGF production and attenuated apoptotic factor expression, promoting instead a pro-survival factor expression profile with the upregulation of p-akt and Bcl-2. These effects were not observed after ET-B blockade, which conversely was harmful to hypoxic podocytes by inducing an increased s-Flt 1 secretion in the cell medium.

The first finding of this study is the beneficial effect of ET-A – not shared by ET-B – receptor antagonist on hypoxic podocytes. Although it is well known that ET-1 favours renal disease progression via the detrimental action of the peptide on podocytes, it is still a matter of debate whether selective ET-A receptor over ET-A/ET-B receptor blockade should be preferred for the treatment of kidney diseases. In an aging-associated glomerulosclerosis model, the ET-A selective antagonism was more effective than non-selective ET-A/ET-B receptor blockade in reversing glomerulosclerosis and attenuating podocyte structural damage [6]. Moreover, selective ET-A receptor and non-selective ET-A/ET-B receptor blockades reduced both albuminuria and glomerular permeability in a model of diabetic nephropathy, but only selective ET-A receptor blockade restored nephrin and podocin expression and decreased glomerular inflammation [7]. By contrast, results from transgenic mice indicated that podocyte-specific deletion of both ET-A and ET-B receptors was protective in diabetic mice, offering the rationale for hypothesizing that dual ET-A/ET-B is more beneficial than single ET-A antagonism [8]. In such a controversial context, the new findings by Harvey et al. add support to the use of selective over non-selective ET-1 receptor blockade for the treatment of chronic RVD.

The second significant finding of this study relates to the mechanism underlying the ET-A antagonist-mediated podocyte protection. Taking advantage of the use of VEGF neutralizing antibodies, Harvey et al. identified VEGF as a pivotal factor for podocyte protection. Taking advantage of the use of VEGF neutralizing antibodies, Harvey et al. identified VEGF as a pivotal factor for podocyte protection. Taking advantage of the use of VEGF neutralizing antibodies, Harvey et al. identified VEGF as a pivotal factor for podocyte protection.

The in vitro approach of this study would represent a potential limitation to its clinical applicability. To this end, additional in vivo investigation is warranted to confirm that ET-A antagonism-mediated podocyte protection is due to VEGF. The unprecedented role of VEGF in mediating the protective effect of ET-A antagonism on hypoxic podocytes proposed by Harvey et al. makes it possible to envision the ET-A receptor/VEGF pathway involvement in other renal diseases characterized by oxidative stress and fibrosis, such as diabetes. Notably, in experimental diabetic nephropathy, a number of studies documented the synergistic renoprotective effect exerted by the association of ET-A receptor antagonism with angiotensin-converting enzyme inhibitors (ACEi) [11, 12]. Such positive preclinical results provided the rationale for current trials in patients. Thus, the investigation of whether the effects of combined ACEi – ET-A receptor antagonism treatment are related to VEGF production in patients in ongoing trials could be an intriguing way forward.

Disclosure Statement

The authors have no conflict of interest to declare.

References


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