Role of Endothelin Receptors for Renal Protection and Survival in Hypertension
Waiting for Clinical Trials

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Hypertension causes mesangial cell growth and glomerulosclerosis and is an important cause of chronic renal failure.1 Urinary loss of proteins is determined by dysfunction of the glomerular filtration barrier for which intact function of visceral glomerular epithelial cells (podocytes) is critical.2,3 Consequently, microalbuminuria and albuminuria have become reliable and early markers of glomerular disease in hypertensive subjects.1,4 In patients, treatment of hypertension with several types of drugs, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers but also calcium antagonists or β-blockers, delays the development of renal disease,4 and under certain conditions, proteinuria may actually regress.5 Experimental models of hypertensive renal disease show that established proteinuria and glomerulosclerosis may even be reversed by some drugs.6 However, in the majority of these studies, the drugs also had pronounced antihypertensive effects; thus, pressure-lowering effects of the drugs possibly also contributed to glomerular “healing.”7

Mimicking activation of the renin–angiotensin–aldosterone system (RAAS) in rats by infusion of angiotensin II results in hypertension and pronounced vascular hypertrophy;8,9; renal and vascular endothelin (ET)-1 synthesis also increases, suggesting an interaction between ET and the RAAS.8 This link is further strengthened by studies showing that ET A receptor blockade completely normalizes the structural changes in the vasculature induced by angiotensin II, despite only partially reducing blood pressure.9 Even salt-sensitive hypertension induced by angiotensin II seems to depend on the ET system.10

The interaction between these systems has been investigated further using a genetic model of RAAS-dependent hypertension, a transgenic rat model carrying the mouse renin 2 gene.11 This model of renin-dependent hypertension is characterized by malignant hypertension, and untreated animals die prematurely because of myocardial infarction, heart failure, and stroke.11 Previous studies have investigated the effects of ET blockade on hypertension and target organ injury in this model, but the data available have shown inconsistent effects.12–14 To study the interdependency of hypertension and end organ damage clearly, a “next-generation” transgenic rat model of hypertension in which RAAS-dependent hypertension can be turned on and off at the discretion of the researcher has become available recently15 and provides a very powerful and flexible new model that significantly extends the experimental possibilities afforded by the traditional TGR(mRen2) 27 strain. Not only can therapeutic intervention be initiated in the normotensive, rather than the prehypertensive state, but the degree of blood pressure rise can be determined experimentally providing powerful tools for studies relating the RAAS with the ET system.

In a previous prevention study, Vaněčková et al16 have shown that in traditional Ren-2 transgenic rats treated with high-salt diet, pharmacological blockade of either or both ET A and ET B (ET b) or only the ET A receptor improved renal and left ventricular structure, whereas only ET A receptor blockade had antihypertensive effects. In the present issue of Hypertension, this group extends their previous report, presenting results of a study in which treatment was begun after substantial hypertension had already developed, an approach that is much closer to the clinical situation. Untreated animals showed a high mortality, podocyte injury, thickened glomerular basement membranes, and proteinuria but not yet glomerulosclerosis.17 Although there was an initial drop in blood pressure of animals treated with the ET A antagonist, by the end of treatment, there was no difference in the hypertension between different treatment groups. Blood pressure was measured either by the tail-cuff method or under anesthesia, and small effects of the drug on blood pressure might not have been detected. Nevertheless, only selective blockade of the ET A receptor but not of both ET A and ET B receptors (despite having similar effects on blood pressure) had a striking effect on survival and elevated cardiac ET levels and seemed to have normalized glomerular capillary structure and prevented or reversed podocyte injury and proteinuria.17

The findings by Opočenský et al17 are remarkable for several reasons: (1) this study for the first time demonstrates beneficial effects of ET A blockade with atrasentan on animal survival and podocyte structure in the face of sustained hypertension; (2) the beneficial effects of treatment on podocyte and glomerular capillary structure and proteinuria occur even before the development of glomerulosclerosis, which, in this animal model, only develops at a later stage.
after prolonged hypertension\textsuperscript{18}; and (3) although in rodents and humans the ET\textsubscript{B} receptor is the predominant receptor in the kidney, only selective blockade of the ET\textsubscript{A} receptor was fully effective. Indeed, blockade of both receptors was considerably less effective for animal survival than selective ET\textsubscript{A} receptor blockade. It seems, therefore, that ET-1 can exert pressure-independent damage via activation of ET\textsubscript{A} receptors and that activity at ET\textsubscript{B} is beneficial. Pressure-independent, deleterious effects of ET\textsubscript{A} receptor activation have been noted in normotensive aged rats where darusentan, another ET\textsubscript{A} receptor selective antagonist, reverses preexisting proteinuria, podocyte injury, glomerular capillary hypertrophy, and glomerulosclerosis\textsuperscript{19} and is associated with expression changes of the cyclin-dependent kinase inhibitor p21\textsuperscript{WAF1/CIP1}.\textsuperscript{19} Marked improvements of podocyte injury were also seen in other models of hypertension after aldosterone antagonism\textsuperscript{19–21} but not after treating hypertension only with hydralazine.\textsuperscript{21} This suggests that the injured podocyte is responsive only to certain types of treatments can promote recovery of the glomerular filtration barrier.\textsuperscript{22} Because ET-1 (via activation of ET\textsubscript{A} receptors)\textsuperscript{19,23} or angiotensin II\textsuperscript{24} cause disruption of the podocyte filamentous actin cytoskeleton, blockade of these systems may well be beneficial, stimulating podocytes to promote endothelial cell growth\textsuperscript{25} or regeneration of glomerular capillaries.\textsuperscript{25,26} In view these observations and the findings now presented by Opočenský et al,\textsuperscript{17} it now seems likely that inhibition of the pathways controlling podocyte and glomerular capillary structure are reversible and effective even in the presence of sustained hypertension (Figure).

The results reported by Opočenský et al\textsuperscript{17} also point at a clear role for the ET\textsubscript{B} receptor having an important vascular and renal back-up function as demonstrated previously under salt-sensitive conditions.\textsuperscript{27,28} It is, therefore, likely that both salt-dependent and ET\textsubscript{B} receptor–dependent mechanisms were involved in the beneficial effects of ET\textsubscript{A} receptor blockade. The improvement of survival may also be because of the effects of ET\textsubscript{A} antagonists functioning as partial angiotensin-converting enzyme inhibitors in the kidney.\textsuperscript{29} Another interesting aspect of the study by Opočenský et al\textsuperscript{17} is that the degree of histological podocyte injury reported, rather than the hypertension, paralleled and was correlated with mortality. Despite some limitations of the morphometric techniques used (no determination of filtration slit density nor determination of true harmonic glomular basement membrane thickness) and a disconnection between histological alterations and proteinuria status, these data are consistent with the podocyte being an effective sensor of stress in the entire vascular bed of the animal. This may be of strong clinical relevance, because urinary excretion of podocytes or podocyte membranes is a highly sensitive marker for renal injury,\textsuperscript{30,31} and microalbuminuria as the first sign of glomerular filtration barrier failure is a strong predictor of cardiovascular mortality in humans.\textsuperscript{32} Possibly, improvements in glomerular basement membrane structure seen after ET blockade in hypertensive\textsuperscript{17} and normotensive\textsuperscript{19} animals also contribute to the reduction in proteinuria even before podocyte injury occurs.\textsuperscript{33} This would also explain the dissociation between the degree of podocyte injury and proteinuria status reported by Opočenský et al.\textsuperscript{17}

To test the therapeutic potential of ET antagonists for hypertension and renal disease in patients, clinical studies are needed. A first study initiated by Speedel pharmaceuticals using their newly developed ET\textsubscript{A} receptor antagonist avosentan (SPP301) added to standard therapy showed pronounced antiproteinuric effects in diabetic subjects with a reduction of proteinuria of >40\% after 12 weeks,\textsuperscript{34} and a phase III trial, the randomized, placebo-controlled Avosentan on Doubling of Serum Creatinine End Stage Renal Disease and Death in Diabetic Nephropathy Trial (ASCEND Trial), is now underway to test the therapeutic efficacy in a larger population of diabetics with diabetic renal failure who often also require antihypertensive therapy.\textsuperscript{35} Myogen Inc most recently an-
nounced the initiation of a phase III trial using the ETα antagonist darusentan (LU135252) in patients with “resistant” hypertension.36 Hypertension resistant to conventional antihypertensive treatment in humans is frequently associated with salt sensitivity for which, at least experimentally, darusentan has been shown to provide substantial organ protection.37,38 In the Fixed Doses of Darusentan as Compared With Placebo in Resistant Hypertension Trial (DORADO Trial), darusentan will be given to patients in whom goal blood pressure though an appropriate 3-drug maximum dose regimen could not be achieved and who are likely to also have hypertensive renal injury. Hopefully, these clinical studies will provide answers to the questions of whether ETα receptor antagonists can provide similar therapeutic benefits to humans as in experimental studies and whether such benefits might translate into an improvement of morbidity and mortality in patients with hypertension and renal disease.

Sources of Funding
This work was supported by the Swiss National Foundation (SNF 3200-058426.99, 3232-058421.99, and 3200-108258/1) and the Wellcome Trust.

Disclosures
None.

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Hypertension. 2006;48:834-837; originally published online October 2, 2006; doi: 10.1161/01.HYP.0000245138.09687.8a
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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