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REVIEW

Endothelin Receptors Antagonists as Renal Protective Agents

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Abstract: Endothelin (ET) is an important modulator of renal function through its binding to ET_A and ET_B receptors in renal tissue. Various renal cells have the ability to synthesize and release endothelin-1 and elevated plasma and urinary endothelin levels have been measured in patients with chronic kidney diseases. Within the last 5 year, several studies have demonstrated that ET plays a role in the pathogenesis and progression of chronic kidney diseases and associated cardiovascular diseases. With this increasing evidence, several ET receptor antagonists have been developed, some of them being specifically investigated for their ability to provide renal protection in diabetic nephropathy. For this indication, a selective blockade of ET_A receptors appears to be the preferred approach. Thus, recent clinical phase II and phase III studies have shown that ET_A receptor blockers such as avosentan are able to lower proteinuria significantly in type 2 diabetic patients even on top of a full treatment with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers. However, today, the clinical benefits of ET receptor antagonists appear to be limited by the development of fluid retention and peripheral edema which have been reported to occur with all antagonists, but more so with non-selective ET antagonists. Fluid retention, like headache, nausea and nasal congestion probably represent class side-effects. Nevertheless, provided a good equilibrium can be obtained between their clinical benefits and their tolerability profile, ET receptor blockers remain promising for the management of patients with chronic kidney diseases.

Keywords: humans, renal hemodynamics, sodium excretion, blood pressure, avosentan

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Introduction

Endothelin (ET), the most potent vasoconstrictor known, was discovered in the late eighties by Yanagisawa et al.[1,2] In humans, the ETs comprise three 21-amino acid vasoactive peptides (ET-1, ET-2 and ET-3), formed from the prepro- and big-endothelins. The three ET isoforms bind to two cell-surface receptors, ET receptor subtypes A (ET_A) and B (ET_B), which have antagonizing effects. ET_A receptors have primarily vasoconstrictor and growth-promoting functions, whereas ET_B receptors mainly mediate vasodilatation and inhibition of growth and inflammation, via release of nitric oxide and prostacyclin. The ET_B receptor also functions as a clearance receptor for ET and affects fluid and electrolyte transport in the renal tubule. The ET_A receptor has its highest affinity for ET-1, followed by ET-2 and ET-3, with all the ETs exhibiting equal affinity for the ET_B receptor. In humans, ET-1 is the predominant isoform of the endothelins and acts as an autocrine and paracrine system.[3] It is mainly derived from endothelial cells and thus, is involved in the physiology and pathophysiology of almost all organs including the heart, lung, kidneys and brain.[4]

Endothelin in the Normal Kidney

Endothelin-1 is an important modulator of renal function via its binding to abundant ET receptors in renal tissue and by the ability of various renal cells to synthesize and release ET-1.[5] This was elegantly demonstrated by the infusion of exogenous ET-1 in humans:[6] when infused intravenously ET-1 induced a significant renal vasoconstriction as demonstrated by a fall in total renal blood flow (RBF) and reduction in glomerular filtration rate (GFR). The renal vasculature was shown to be more sensitive to the vasoconstricting effects of ET-1 than other vascular beds.[7]

In renal resistance vessels the majority of ET-1 production occurs in endothelial cells. The vascular smooth muscle cells express both ET_A and ET_B receptors which regulate vascular tone. Most endothelial cells express only ET_B receptors, and autocrine activation of the endothelial cell ET_B receptor induces production of prostaglandins (mainly PGI_2) and nitric oxide (NO), which tend to counteract the vasoconstrictor effect of ET-1.[8]

Glomerular endothelial, epithelial and mesangial cells also synthesize, bind and respond to ET-1. ET-1 is produced by glomerular endothelial cells and podocytes, thus acting potentially on both sides of the glomerular basement membrane as well as on the slit diaphragm.[8,9] There is good evidence that ET-1 directly and indirectly stimulates mesangial cell mitogenesis as well as partially mediating the proliferative response to other growth factors. In mesangial cells, proliferation, hypertrophy, contraction and extracellular matrix accumulation are mainly mediated by ET_A receptors.[10]

Renal tubule-derived ET-1 regulates cell proliferation, extracellular matrix accumulation and indirectly regional blood flow.[8,11] In the renal tubule, ET-1 modulates fluid and electrolyte transport as well as acid-base balance. The collecting duct produces more ET-1 than any other cell type in the body, the inner medullary collecting duct being the main renal tubular source of ET-1.[12] However, other tubule segments, including the cortical collecting tubule, the medullary thick ascending limb and the proximal tubule synthesize ET-1. The distribution of ET-receptors in the renal tubule parallels that of ET-1 production. Renal tubules predominantly express ET_B receptors and the activation of these ET_B receptors inhibits sodium and water absorption and causes natriuresis and diuresis in the collecting duct via inhibition of sodium transport via $E_{Na}C$ and AVP-stimulated water transport. In this respect, the tubular endothelin system participates in the negative feedback loop that promotes diuresis and natriuresis and thereby counterbalances the effects of other hormones such as vasopressin and angiotensin II. The role of tubular ET_A receptors in regulating natriuresis is less clear. ET_B receptors possibly modulate H^+ and HCO^{3-} secretion to promote acid-induced urinary acidification.[11] The various functions of endothelin receptors in the kidney are summarized in Table 1.

Endothelin in the Diseased Kidney

Several animal and human studies have suggested that the renal endothelin system plays a role in the pathophysiology of chronic kidney diseases. In animal models with a reduced renal mass, endothelin-1 expression increases and correlates with the extent of proteinuria and structural renal lesions.[13,14] Similarly, increased plasma endothelin levels have been measured in patients with renal diseases when compared with healthy subjects and the amount of endothelin found in urine again

Table 1. Renal localization of endothelin receptors and local function of endothelin.

Localization	ET_A	ET_B	Function
Vessels			
Large renal arteries	++	+	Vasoconstriction ET_A Vasodilation ET_B
Afferent and efferent arterioles	++	+	Afferent vasoconstriction ET_A and $_B$ Efferent vasodilation ET_B Increase in intraglomerular pressure
Medullary vasculature	–	+	Vasodilation ET_B
Vascular endothelium	–	+	Tonic vasodilatory effect
Glomerulus			
Mesangial cells	+	(+)	Contraction, proliferation, ECM production, migration, MCP-1 production
Endothelial cells	–	++	NO and prostaglandin production?
Podocytes	++	(+)	Reduced expression of nephrin and synaptopodin, cytoskeletal reorganization
Tubular cells			
Proximal tubule	–	++	Increase in acid secretion Negative regulation of angiotensin AT1 receptors
Descending + ascending thin limb	+	+	
Thick ascending limb	–	++	Production of NO and prostaglandins; Inhibition of Na reabsorption through NKCC2
Cortical and outer medullary collecting duct	(+)	++	Distal nephron acidification Inhibition of vasopressin action
Inner medullary collecting duct	+	++++	Natriuresis and diuresis

Adapted from references 5 and 25.
Abbreviations: ECM, extracellular matrix; MCP-1, monocyte chemoattractant protein-1; AT 1, angiotensin receptor type 1; NO, nitric oxide; NKCC2, Sodium-potassium-two chloride channel.

correlated with the severity of proteinuria.[15] Direct evidence for a causal role of ET-1 in renal fibrosis has been shown in transgenic mice overexpressing human ET-1.[16] A link between glomerular barrier dysfunction and proteinuria, increased renal production of ET-1 and progressive renal failure has also been reported.[17]

In renal ET_B receptor-deficient *sl/sl* ($ET_B^{sl/sl}$) rats partial ablation causes higher and earlier increases in blood pressure (BP), progression of renal functional insufficiency, severe glomerular and tubular lesions, enlargement of glomeruli, and cardiovascular hypertrophy compared with wild-type ($ET_B^{+/+}$) animals.[18] Another rat model deficient in renal ET_B receptors developed a salt-sensitive hypertension, with restoration of normal BP by amiloride, suggesting that the ET_B receptor regulates sodium excretion at the epithelial sodium channel in collecting duct cells, and hence ET_B receptor antagonist-treated rats develop a sodium-dependent hypertension.[19,20]

In streptozotocin-diabetic rats, glomerular ET-1 expression and urinary ET-1 excretion have been found to be markedly elevated. Studies on primary cultures of rat mesangial cells have also demonstrated that high glucose levels can stimulate ET-1 promoter activity and ET-1 expression.[21] Conversely, glycemic control normalizes ET-1 levels, ET_A receptor expression and attenuates the process of increased collagen synthesis in a rat model of type 2 diabetes.[22]

In several experimental models of nephropathies, ET-1 expression is increased essentially in the glomeruli. Mesangial cells and podocytes appear to be the main source of glomerular ET-1. Hence, the local glomerular release of ET-1 might contribute to the pathogenesis of glomerular injury in diabetes, hypertension and glomerulopathies as ET-1 favors the development

of mesangial proliferation and extracellular matrix production. Of note, these effects appear to be mediated primarily by the activation of ET_A receptors, an observation which provides the rational for developing selective ET_A receptors antagonists for the management of patients with chronic nephropathies.

There are also several other mechanisms whereby endothelin activation might contribute to the progression of renal diseases:[17,23,24] the ET-1 stimulation of mesangial cells induces the release of chemokines such as the monocyte chemoattractant protein-1 (MCP-1) which promotes the monocyte/macrophage infiltration; ET-1 released by mesangial cells and podocytes may affect nephrin and the glomerular barrier leading to a dysfunction of the permselectivity an effect which may also be mediated by activation of ET_A receptors. The release of ET-1 by tubular cells triggered in part by the reabsorption of filtered proteins may contribute to the recruitment of inflammatory cells in the renal interstitial tissue and hence participate in the proliferation of fibroblasts and development of interstitial fibrosis. At last, ET-1 interacts with several other pathogenic mechanisms involved in the progression of renal diseases such as the renin-angiotensin system and transforming growth factor.

Taken together, these data suggest that in addition to its physiological role, an excessive renal production of ET-1 may represent an important pathogenic mechanism in renal diseases. The experimental evidence gathered during the recent years in experimental nephropathies has set the basis for the investigation of selective endothelin receptor antagonists in the management of chronic kidney diseases.

Pharmacology of Endothelin Receptor Antagonists

The first report of an ET receptor antagonist (ERA) came only 2 years after the discovery of ET. ERAs have been classified as selective for ET_A or ET_B receptors or nonselective dual antagonists. The distinction between selective and dual ERAs is not clearly defined. It is generally agreed that selective ET_A receptor antagonists have more than 100-fold selectivity for the ET_A receptor.[5,25,26] The first widely used ERAs were BQ-123, a selective ET_A receptor antagonist, and BQ-788, a selective ET_B receptor antagonist. These peptide antagonists have been useful for defining the pathophysiology of the ET system, but their high cost and parenteral administration has stopped their use in large clinical trials. Bosentan (pyrimidinesulfonamide), a dual ERA, was the first ERA used in large clinical trials and drug development and is now used in patients with pulmonary arterial hypertension (PAH). There are now several selective and dual ERAs in the "-sentan" class of drugs that have been or are being studied, for example ambrisentan and darusentan (propanoic acid), atrasentan and enrasentan (carboxylic acid), avosentan, clazosentan and tezosentan (pyrimidinesulfonamide), and sitaxsentan (biphenyl sulfonamide) (Table 2).[27] Beyond PAH, these compounds have been evaluated in several other indications including heart failure, severe or resistant arterial hypertension, prostate cancer, malignant glioma and sclerodermia.[28] In arterial hypertension, significant decreases in BP have been obtained with endothelin antagonists, particularly among patients with resistant hypertension.[29,30] However, long-term studies are still missing with these agents. BQ-123, BQ-788 and avosentan have been used in humans to investigate the concept of ET receptor blockade in the kidney in health and disease with a special emphasis on diabetic nephropathy.

Endothelin Receptor Antagonists and the Kidney

Animal studies

Numerous animal studies have investigated the potential impact of selective or non-selective endothelin

Table 2. Nonpeptide endothelin receptor antagonists and their relative selectivity for endothelin receptors.

Drug name	Chemical class	Relative selectivity ET_A/ET_B
Bosentan	Pyrimidine-sulfonamide	20
Tezosentan	Pyrimidine-sulfonamide	30
Avosentan	Pyrimidine-sulfonamide	50–600
Enrasentan	Carboxylic acid	110
Darusentan	Propanoic acid	130–170
Ambrisentan	Propanoic acid	200
Clazosentan	Pyrimidine-sulfonamide	1000–3200
Atrasentan	Carboxylic acid	1860
Sitaxsentan	Heteroarylsufonamide	7000
Edonentan	Biphenylsulfonamide	80000

Adapted from reference 27.

receptor antagonists (ERA) in the development of renal diseases as reviewed recently.[5] Thus, in a model of renal mass reduction, treatment with a selective ET_A receptor antagonist has been found to lower urinary protein excretion, to limit glomerular injury, and to prevent renal dysfunction. Selective ET_A receptor blockade has been reported to blunt the rise in BP, to attenuate the development of glomerulosclerosis and vascular hypertrophy in chronic renal failure. Treatment with nonselective ET_A/ET_B receptor antagonists has also shown to prevent the development of glomerular injury in uremic rats. Interestingly, studies have shown that the beneficial effects of an ET_A receptor antagonist on proteinuria and renal dysfunction in partial ablation-induced chronic renal failure rats can be reversed by the concomitant administration of a selective ET_B receptor antagonist.[31]

ERAs have demonstrated renoprotective effects in experimental models of diabetic and non-diabetic nephropathy, independent of their effects on BP.[32] Experimental data suggest that ET_A receptor antagonists may preserve renal function in diabetic rats.[33,34] The antifibrotic effects of ERAs in experimental disease which lead to a reduced proteinuria, renal fibrosis, and increased survival are mainly ET_A receptor mediated.[35] Macrophage infiltration in renal tissue and urinary TGF-β and prostaglandin E2 metabolites can be reduced using an ET_A selective antagonist, an effect that is associated with a reduction in albuminuria in rats with streptozotocin-induced diabetes. This indicates that the activation of renal ET_A receptors mediates renal inflammation and TGF-β production in diabetes.[36] ERAs have also been shown to improve endothelial function, reduce inflammation and fibrosis, and reverse vascular remodeling.

Angiotensin II (Ang II) is another powerful vasoconstrictor involved in the regulation of vascular tone, and there is evidence for an interaction between the endothelin and the renin-angiotensin system. Thus, a study in rats has demonstrated that endothelin mediates some of the renal actions of acutely administered Ang II.[37] Further animal data suggest that the concomitant blockade of endothelin and angiotensin-converting enzyme (ACE) inhibition produce BP-independent additive effects on slowing progression in a model of subtotal renal ablation as indicated by better glomerulosclerosis indices and lower proteinuria in animals receiving the endothelin antagonist.[32] This would suggest that there is a potential benefit of adding an endothelin receptor antagonist in renal patients receiving a blocker of the renin-angiotensin system to protect their renal function.

Endothelin Receptor Blockade in Healthy Subjects

In healthy subjects, selective ET_A receptor antagonism produces vasodilatation and reduction in BP, whereas selective ET_B receptor blockade is associated with vasoconstriction, and a pressor response.[38–40] In the healthy kidney, renal vasoconstriction provoked by ET-1 infusion is mediated via the ET_A receptor whereas ET_B receptor activation leads to a medullary vasodilation. Nevertheless, there is no effect of ET_A receptor antagonism alone or dual blockade on glomerular filtration rate and effective renal plasma flow in healthy subjects although systemic BP tends to decrease with the repeated administration of a selective ET_A receptor antagonist.[38,41] In contrast, selective ET_B receptor blockade produces a clear renal vasoconstriction.[38] This would indicate that the ET_A receptor is important for the maintenance of vascular tone and BP but less so for the regulation of renal vascular tone in healthy individuals. In contrast, the ET_B receptor is important to maintain a tonic vasodilatation of the renal vasculature.

A study in healthy subjects has investigated the renal hemodynamic effects of combining an ET_A receptor antagonist and an ACE inhibitor.[42] They have shown that the two drugs act synergistically through an ET_B receptor-mediated, NO-dependent, and COX-independent mechanism. The association reduced mean arterial pressure, increased effective renal blood flow, reduced effective renal vascular resistance and increased urinary sodium excretion. This finding further supports the potential interest of combining the two therapeutic approaches in humans.

Endothelin Receptor Blockade in Renal Diseases

Diabetic nephropathy is the major cause of end stage renal disease (ESRD). Patients with diabetes have elevated circulating ET-1 levels; both plasma and urinary ET-1 levels are elevated in patients with diabetes and ET levels correlate with reduced renal function, increased BP and albuminuria, and severity and

duration of diabetes.[43] Proteinuria has emerged as a powerful predictor of renal disease progression, and proteinuria reduction is important to prevent renal functional loss. Moreover, albuminuria is strongly associated with increased cardiovascular risk in both individuals with hypertension and individuals with no known risk factor. As discussed above, an excessive ET-1 production might be implicated in both the development and progression of CKD and associated cardiovascular diseases.[44] The association between CKD and cardiovascular disease is strong, and most patients with renal diseases die from cardiovascular complications before they develop end stage renal disease.

Several studies have investigated the potential benefits of endothelin antagonists in patients with CKD.[28,38,45–47] A comparison of selective and dual endothelin receptor blockade with BQ-123 or BQ-788 or the combination of BQ 123/788 in 8 patients with stage 2–3 CKD has shown that selective ET_A receptor blockade with BQ-123 reduces BP and effective renal vascular resistance, and increases renal blood flow more than dual blockade with BQ-123/788. The effects of ET_A receptor blockade and dual blockade on systemic hemodynamics were similar but less pronounced in healthy subjects than in patients, and there were no effects on renal hemodynamics in healthy subjects. Selective ET_A receptor blockade also reduced the effective filtration fraction (EFF) and urinary protein excretion in patients (–46%), suggesting a potential renoprotective effect. ET_B receptor blockade alone with BQ-788 produced substantial systemic and renal vasoconstriction in both patients and healthy subjects. Surprisingly no changes in sodium excretion or fractional excretion were observed, even though there is evidence for ET_B receptor-mediated natriuresis in animal studies.

In a more recent study including 22 patients with stable proteinuric stage 3 CKD, ET_A receptor blockade with BQ-123 reduced BP, arterial stiffness and proteinuria by 30%.[46] These effects were obtained on top of maximally tolerated treatment with ACE inhibitors and angiotensin receptor blockers (ARBs). The reduction in proteinuria and arterial stiffness were greater than those found with an alternative method of BP reduction. Thus the study confirmed the importance of ET-1, acting through the ET_A receptor, in maintaining the increased vascular tone seen in CKD and provided additional evidence that ET receptor antagonism may represent a novel strategy to lower BP and proteinuria in CKD patients. Of note, in this study, renal blood flow increased but there were no significant changes in GFR. This lead to a significant decrease in filtration fraction as reported in other studies.

Avosentan is an orally available ET_A antagonist in clinical development for the treatment of diabetic nephropathy. A reduction in urinary albumin excretion in patients with diabetic nephropathy was demonstrated following chronic ET_A receptor blockade (12 weeks) with avosentan on top of standard treatment with ACE inhibitors and/or ARBs.[47] Doses of 5, 10, 25 and 50 mg or placebo were used in 286 randomly assigned patients with stage 2 CKD. The decrease in albumin excretion rate (UAER, mg/min) between baseline and week 12 was >30% in all four avosentan treatment groups, considered to be a clinically significant reduction. No change in blood pressure was observed in this study. The main adverse event was peripheral edema (12%), mainly with high (>25 mg) doses of avosentan. There was no data on urinary sodium excretion in this study.

The largest trial in patients with diabetic nephropathy, the ASCEND trial, was also conducted with avosentan. In this placebo-controlled multicenter phase III morbidity and mortality study, avosentan doses of 25 and 50 mg or placebo were administered once daily to type 2 diabetic patients with albuminuria and stage 3-4 CKD on top of standard treatment with ACE inhibitor or ARB. 2364 patients were randomized and the primary endpoints were time to doubling of serum creatinine, ESRD or death. Secondary endpoints included changes in proteinuria, GFR and cardiovascular events. This study was stopped prematurely after 18 months for safety reasons, with median treatment duration of 3 months. Although avosentan significantly lowered proteinuria (–45 to –50% after 3–6 months of treatment) independently of BP, there were noticeably more cardiovascular events (i.e. fluid overload and congestive heart failure) in the avosentan groups than in the placebo group (Viberti G, et al. Efficacy and safety of the endothelin receptor antagonist Avosentan in diabetic nephropathy (ASCEND study) [Abstract]. *J Am Soc Nephrol.* 2008;19:478). This finding is not totally surprising as fluid retention resulting in headache, peripheral edema, weight gain,

and in some cases worsening of congestive heart failure has been reported with several other non-selective endothelin receptor antagonists. Most of the adverse events have been related to non-specific vasodilating effects linked to ET_B receptor blockade, but the actual mechanisms of the peripheral edema and fluid overload remain unclear.

To investigate whether peripheral edema and fluid retention could result from a renal retention of sodium and water, we conducted a placebo-controlled cross-over study in 23 healthy male subjects to assess the acute and sustained renal hemodynamic and tubular effects of avosentan and the dose dependency of these effects.[41] Oral avosentan was administered once daily for 8 days at doses of 0.5, 1.5, 5, and 50 mg. The drug induced a dose-dependent median increase in body weight, most pronounced at 50 mg (+0.8 kg on day 8). Doses of 5 and 50 mg induced dose-dependent decreases in diastolic BP, suggesting peripheral vasodilatation. As observed with other antagonists in healthy subjects, avosentan did not affect renal hemodynamics or plasma electrolytes. However, a clear hemodilution due to isotonic fluid retention was seen, particularly at the 50 mg dose. A dose-dependent median reduction in fractional renal excretion of sodium was found (up to 8.7% at avosentan 50 mg), and this reduction was paralleled by a dose-related increase in proximal sodium reabsorption suggesting that avosentan dose-dependently induces sodium retention by the kidney, mainly through proximal tubular effects. Interestingly, the renal tubular effects of avosentan were clearly dose-dependent with virtually no sodium retention at doses below 5 mg per day. Therefore, one concluded that the antiproteinuric effect of avosentan should be investigated at doses <5 mg. Of note, at doses below 5 mg, avosentan is probably very selective for ET_A receptors but the real impact on urinary protein excretion is not well characterized.

A diffuse extravasation of fluids induced by ET receptor blockade might be another potential mechanism whereby endothelin antagonists may promote peripheral edema and eventually lung edema. To test this hypothesis, we infused increasing doses of avosentan in binephrectomized rats and measured the changes in hematocrit over 1 hour (Fig. 1). Interestingly, a concentration dependent extravasation of fluid, as measured by changes in hematocrit, was

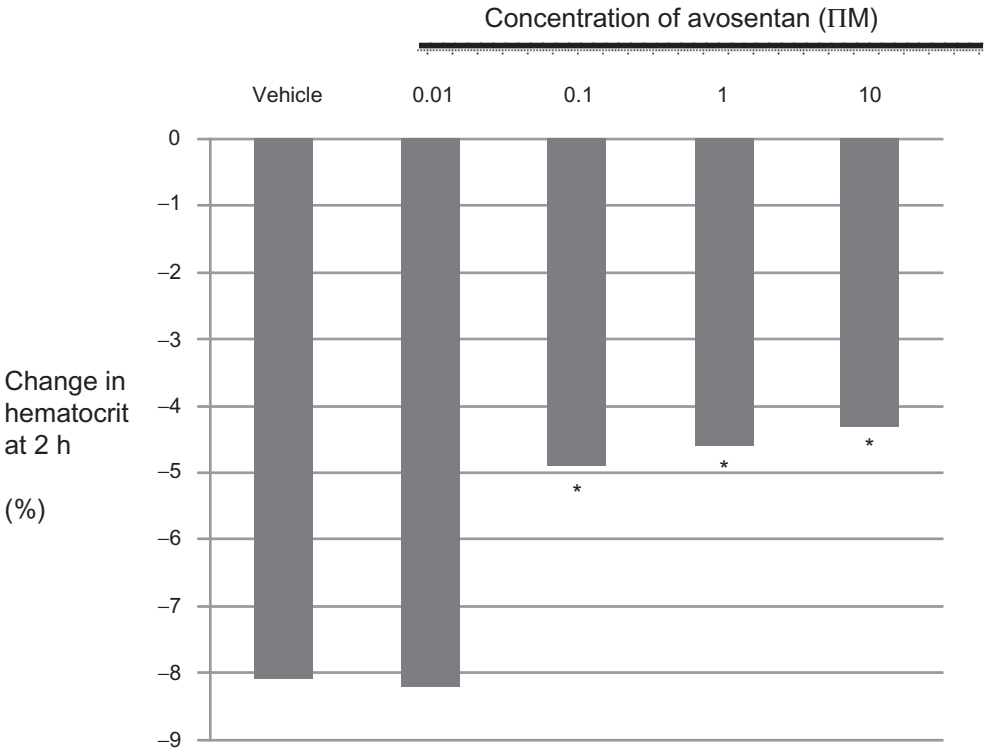

Figure 1. Effect of a 2 h infusion of increasing doses of avosentan in the same volume in binephrectomized rats.
At higher concentrations, avosentan induces a shift of fluid out of the vascular space as reflected by a significantly lesser change in hematocrit despite the same volume of infusion in rats without kidneys.

found suggesting an increased vascular permeability or a precapillary vasodilation as observed with peripheral vasodilators such as calcium channel blockers (Maillard M, et al. Do endothelin receptor antagonists induce edema through an extravasation of fluids? Evidence from an experiment in bi-nephrectomized rats [Abstract]. *J Hypertens.* 2008;26 suppl 1:371). Thus the vasodilatation associated with fluid shift into the extravascular space could further worsen the impact of the renal sodium and water retention induced by endothelin receptor antagonists.

Taken together, the data gathered so far on the mechanisms of the fluid retention observed with several selective ET_A receptor antagonists point on several potential mechanisms including the non-selective blockade of ET_B receptors, a peripheral vasodilatation leading to an extravasation of fluids and an increase in renal tubular sodium reabsorption. Of note, since the highly selective ET_A receptor antagonist sitaxsentan also gives fluid retention, one cannot exclude that ET_A receptor blockade per se promotes sodium retention.[48] However, even with this selective compound, it is not possible to exclude some inhibition of ET_B receptors at certain doses.

Conclusions

More recently, several experimental and clinical studies have demonstrated that ET-1 plays a major role in the regulation of renal function and that endothelin receptor blockers may have a favorable impact on the progression of renal diseases. The most recent clinical data suggest that indeed, selective ET_A receptor blockade may be an effective strategy to decrease BP and proteinuria and hence to slow the progression of chronic kidney diseases. There is also a good rationale for combining this therapeutic approach with blockers of the renin-angiotensin system, as both therapeutic approaches appear to be synergistic. However, the actual challenge of endothelin receptor blockade is to find the right balance between the clinical benefits and the tolerability profile. In order to avoid fluid and sodium retention, compounds should probably be very selective for ET_A receptors though one has not totally excluded that even highly selective ET_A receptor blockers might induce sodium retention and fluid retention. In any case, owing to the increased incidence of diabetic nephropathies in the population and the need for improved therapeutic approaches for this disease, the availability of new drugs which increase our ability to control BP and proteinuria and retard the progression of renal diseases will be most welcome.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

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