Published in final edited form as:

Curr Opin Nephrol Hypertens. 2010 March ; 19(2): 134–139. doi:10.1097/MNH.0b013e328335f91f.

Endothelin, Hypertension, and Chronic Kidney Disease: New insights

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Abstract

Purpose of review—Endothelin is important in the development of cardiorenal pathology. This review discusses recent developments in understanding endothelin's role in hypertension and chronic kidney disease (CKD).

Recent findings—Endothelin-1 production is increased in hypertension and CKD. Endothelin-1 stimulates vasoconstriction, inflammation and fibrosis, thereby promoting hypertension, atherosclerosis and CKD. These effects are closely linked to angiotensin II and reactive oxygen species. In preclinical studies, endothelin receptor antagonists were effective in treating hypertension (particularly with endothelial dysfunction) and CKD. In pre-clinical studies, endothelin A-selective, as opposed to combined endothelin A and B, receptor blockers have generally been more efficacious. Few clinical trials have been conducted in hypertension and/or kidney disease, partly due to concerns over side effects of testicular toxicity and fluid retention. Endothelin blockade reduces blood pressure in patients with resistant hypertension, with additional beneficial metabolic effects. Endothelin antagonism improves proteinuria in CKD (diabetic or not), particularly in patients taking inhibitors of angiotensin II action.

Summary—Endothelin is a promising target in the treatment of resistant hypertension and CKD, with additional potential benefits on atherosclerosis and the metabolic syndrome. The nature and mechanisms of drug side effects require elucidation before the potential of this new class of drugs can be fully realized.

Keywords

Endothelin-1; blood pressure; sodium excretion; kidney disease

Introduction

Endothelin-1 (ET-1) was first identified in 1988 as an endothelial cell-derived peptide with the greatest vasoconstrictor potency of any known endogenous compound. After over 22,000 publications dealing with endothelins, it is apparent that ET-1 exerts multiple biologic effects, including regulation of vascular tone, renal sodium and water excretion, cell growth and proliferation, extracellular matrix accumulation, and others. Such biologic

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The author has no conflicts of interest.

complexity is due to several factors, including: 1) ET-1 is produced by, and binds to, almost every cell type in the body; 2) the two mammalian ET receptors (ETA and ETB) can mediate different biologic effects within the same cell as well as between different cell types; 3) ET-1 functions primarily in an autocrine or paracrine manner (it is mainly secreted abluminally), permitting localized microenvironmental effects; 4) a large variety of factors modulate ET-1 production, including vasoactive mediators, cytokines, growth factors, inflammatory substances and others (Figure 1); and 5) the biologic effects of ET-1 can differ depending upon the amount of ET-1 present. This review focuses on the role of ET-1 in vascular and renal pathology. As will be evident, this peptide has emerged as a key target for drug therapy of hypertension and chronic kidney disease (CKD).

Endothelin in the control of blood pressure

ET-1 affects many systems that impact blood pressure, including central and peripheral nerves, circulating hormones, the vasculature, the heart and the kidneys [1]. Vascular smooth muscle ETA and ETB activation causes vasoconstriction, while endothelial cell ETB activation is vasodilatory mainly due to nitric oxide release. ETB serve a clearance function, hence ETB blockade raises plasma, and presumably tissue, ET-1 concentrations.

ETB activation inhibits sodium transport in the nephron. The collecting duct ET system is particularly important; principal cells synthesize and bind unusually high levels of ET-1 [2], while collecting duct-specific disruption of ET-1 causes salt-sensitive hypertension [3]. Recent studies indicate that the natriuretic and antihypertensive effect of collecting duct-derived ET-1 is partly mediated by nitric oxide [4]. Some perplexing findings relate to studies in mice with collecting duct-specific knockout of ET receptors. Collecting duct ETB knockout mice have salt-sensitive hypertension [5], while collecting duct ETA knockout mice are normotensive [6]. However, collecting duct knockout of both ETA and ETB causes greater hypertension and sodium retention than in mice with only ETB disruption [7]. This suggests that, under certain circumstances, collecting duct ETA may exert a natriuretic effect. This conclusion is supported by recent studies in which renal medullary infusion of ET-1 into female rats lacking ETB increased urinary sodium excretion [8]. The mechanisms are unknown by which nephron ETA exerts a natriuretic effect, however further clarification of this pathway is of clinical relevance. To my knowledge, every ET receptor antagonist used in humans and experimental animals, whether a combined ETA/ETB blocker or purportedly ETA-selective, causes hemodilution and edema, strongly suggestive of fluid retention [9]. Indeed, such fluid retention may have been partly responsible for the failure of ET antagonists to benefit patients with congestive heart failure [1]. A recent phase III trial studying the effect of avosentan (relatively ETA selective) on renal function in patients with diabetic nephropathy was discontinued due to excessive fluid retention [10]. A follow-up study determined that avosentan dose-dependently reduced urinary sodium excretion in normal individuals [11]. While it remains to be determined if avosentan blocked ETB, particularly at the higher doses, the above results indicate that blocking renal ETB, and probably also ETA, reduces sodium excretion. Determining the mechanisms responsible for ET antagonist-induced fluid retention, and development of appropriate interventions, is clearly important to the future clinical utility of this class of drugs.

Endothelin in hypertension: pre-clinical studies

Numerous studies in animals or humans have implicated ET in the pathogenesis and/or maintenance of hypertension [1,12,13] (figures 1 and 2). In the setting of hypertension, ET-1 increases vasoconstriction and promotes vascular remodeling. The increased vasoconstriction relates to elevated ET-1 production, neurohumoral potentiation and/or downregulation of vasodilators such as nitric oxide. Both ETA and ETB have been

implicated in the elevated vasoconstrictor response to ET-1 in hypertensive patients. Interestingly, ET-1-dependent vascular tone increases with aging, even in normotensive individuals (although the older patients had higher blood pressure than younger ones); this effect was via ETA activation and could be reversed by regular aerobic exercise [14]. The enhanced role for ET-1 in vascular tone with aging may relate to the well documented increase in reactive oxygen species; ET-1 can increase, as well as be increased by, oxidative stress [15,16]. In this regard, it is notable that plasma ET-1 levels inversely correlate with plasma antioxidant status in elderly individuals [17].

Other findings suggest a role for ET-1 in uric acid and fructose feeding associated hypertension. Rats fed a high fructose diet developed hypertension that was ameliorated by bosentan, a nonselective ET receptor antagonist [18]; bosentan also reduced plasma angiotensin II (AII) levels. While the effect of targeting the ET system in uric acid related hypertension have not been examined, in vitro studies found that uric acid stimulates ET-1 gene expression in smooth muscle cells [19] and cardiomyocytes [20]. In keeping with the findings described above for aging, antioxidants suppressed uric acid-stimulated ET-1 synthesis by both cell types. Further, mutation of the AP-1 binding site in the ET-1 gene prevented uric acid induction of ET-1 production; this finding is consistent with the known effect of reactive oxygen species to activate jun and fos that bind AP-1 [20].

Perhaps the greatest pathophysiological impact of ET-1 in hypertension relates to its effects on vascular remodeling. ET-1, via ETA activation, and in cooperation with AII, promotes vascular cell hypertrophy, hyperplasia, inflammatory cell infiltration, and fibrosis. In animals, ETA or nonselective ET receptor blockade reduces atherosclerosis [1,12]. No long-term clinical trials have been conducted to date on the effect of ET antagonism on atherosclerosis; such studies will be of great importance.

Endothelin in hypertension: Clinical trials

Only a few clinical trials have been completed using ET receptor blockade in systemic hypertension. The relative paucity of such trials relates, at least in part, to the side effect profile of this class of drugs [9]. First, ETA or ETB blockade is absolutely contraindicated in pregnancy due to teratogenic effects. Second, initial studies with bosentan were associated with hepatotoxicity, albeit modest (newer ET antagonists, particularly ETA blockers, do not appear to have this complication). Third, although the data has unfortunately never been published other than in company literature, ET antagonists caused testicular toxicity in some experimental animals and reduced sperm counts in some patients. Finally, as discussed above, ET blockade is associated with fluid retention. Thus, given the already broad array of antihypertensive agents, the clinical utility of ET antagonists will most likely be limited to a specific subset of hypertensive patients in whom the benefits outweigh the risks. Such patients most likely have resistant hypertension, particularly those with atherosclerosis. A recent phase III randomized trial (termed DORADO) using darusentan (relatively ETA selective) in 379 patients found a dose-dependent reduction in systolic (−18.1 mmHg) and diastolic (−10.7 mmHg) pressure after 14 weeks of treatment in patients with resistant hypertension (on at least three other antihypertensive agents, one of which was a diuretic) [13]. Another randomized trial involving 72 normotensive patients found that atrasentan (ETA selective) reduced mean blood pressure by 12 mmHg after 6 months in individuals with multiple cardiovascular risk factors and non-obstructive coronary artery disease [21]. In addition, compared to placebo, atrasentan decreased fasting glucose, glycosylated hemoglobin, triglyceride, lipoprotein A and uric acid levels. In a subgroup not treated with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), atrasentan decreased serum creatinine concentration. Finally, no progression of angiographic coronary artery disease was detected in either atrasentan or placebo groups. Side effects

were minimal, however testicular toxicity was not assessed. Thus, ET blockers may fill an important clinical niche, particularly in patients with resistant hypertension, metabolic syndrome and atherosclerosis. No trials have compared ETA with nonselective ET receptor antagonists in such patients, however the pre-clinical data suggests that ETA blockers hold the greatest promise in this regard.

Endothelin in chronic kidney disease - pre-clinical studies

Many studies have demonstrated that the ET system is important in the pathophysiology of chronic kidney disease (CKD) [22–24] (Figures 1 and 2). First, renal ET-1 production is increased in virtually every form of CKD in humans and experimental animals. In hypertensive patients, plasma ET-1 also correlates with renal dysfunction [25]. Similarly, plasma ET-1 levels directly correlated with serum creatinine and degree of albuminuria in patients with diabetic nephropathy [26]. Second, like in the vasculature, ET-1 stimulates fibrosis, cell proliferation and inflammation in the kidney; the peptide can exert pathologic effects on every glomerular cell type and tubule cells. Third, ET receptor antagonists reduce renal injury and disease progression in multiple models of CKD, whether due to diabetes, autoimmune, high renin- or mineralocorticoid-dependent hypertension, reduced renal mass, and other causes.

Multiple mechanisms are responsible for elevated renal ET-1 production in CKD. Renal ET-1 synthesis is stimulated by cytokines, growth factors, chemokines, vasoactive factors, hormones, reactive oxygen species, cholesterol and other substances [22] (Figure 1). Protein overload stimulates proximal tubule ET-1 production, an event that may be of critical importance in renal disease progression [22,27]. In addition, ET-1 can induce nephrin loss from podocytes [28], thereby potentially impairing slit diaphragm function. High dietary protein, through induction of metabolic acidosis, decreases GFR in rats with reduced renal mass [29]. The high protein diet caused primarily tubulointerstitial injury, a finding in keeping with the known effect of metabolic acidosis to induce nephron ET-1 production [30]. An interesting recent study found that chromogranin A, which is released by sympathetic nerves and chromaffin cells, stimulates glomerular endothelial cell ET-1 release which, in turn, enhanced TGF- β 1 production by mesangial cells [31]. This group found that plasma chromogranin directly correlates with plasma ET-1 and inversely with GFR. Furthermore, a chromogranin promoter haplotype predicted the rate of GFR decline. Taken together, the above findings indicate that a truly impressive array of factors can enhance renal ET-1 production. Since excessive renal ET-1 is clearly pathogenic in the kidney, it begs the question as to why the peptide is induced by so many different mechanisms. While the reasons are not fully known, the very fact that ET-1 is produced by virtually every renal cell type, and that such synthesis can be under unique control in each cell type, sets the stage for this potent injurious peptide to be overproduced by a wide variety of conditions and stimuli.

Endothelin in chronic kidney disease – metabolic syndrome and diabetes

ET-1 induced renal injury in the context of the metabolic syndrome and diabetes deserves special mention. Insulin, whether in the setting of frank diabetes or insulin resistance, stimulates both the production and the action of ET-1 in experimental animals and/or in humans [32]. The insulin-stimulated ET-1 production is due, at least in part, to phosphoinositide-3-kinase-dependent activation of glycogen synthase-3 β [33]. Insulin potentiation of ET-1 action was recently shown to involve an interaction with AII since losartan blunted the enhanced ETA-mediated vasoconstriction in insulin-treated diabetic rats [34]. Such an interaction with AII was highlighted in recent studies in diabetic rats wherein renal damage actually regressed when avosentan and lisinopril were given together, but not

separately [35]. These findings are further supported by the observation that ET antagonism reduced renal fibrosis in an animal model of severe AII-dependent hypertension [36].

Endothelin in chronic kidney disease – clinical trials

No long-term studies have assessed the effect of ET antagonists on CKD progression. However, ET blockers have a substantial antiproteinuric effect. The ASCEND trial, involving over 1300 patients, reported up to a 50% reduction in albuminuria after 3 or 6 months of avosentan therapy in patients with diabetic nephropathy on ACEI/ARB treatment [10]. Unfortunately, as discussed earlier, this trial was terminated due to fluid retention. A follow-up study by this group involving 286 patients with diabetic nephropathy on ACEI/ARB therapy, using lower doses of avosentan, noted up to a 30% decrease in albuminuria after 12 weeks of treatment [37]. A recent study found that acute ETA blockade decreased proteinuria by about 30% in non-diabetic CKD patients [38]; blood pressure was similarly lowered by nifedipine, however this increased proteinuria by 26%. In keeping with the concept of an interaction with AII, a follow-up analysis by this group found that the magnitude of proteinuria reduction was greatest in patients on combined ACEI/ARB therapy [39]. Thus, while only proteinuria has been assessed to date, ET antagonism has exciting potential as a therapy in CKD.

Endothelin in chronic kidney disease – which receptor(s) to target?

Several studies have compared the effects of ETA-selective with combined ETA/B antagonists in various models of CKD, including hypertension, high dietary protein and reduced renal mass, as well as acutely in hypertensive patients with CKD [23]. In almost every instance, ETA, as compared to combined ETA/B, blockade has achieved superior results (GFR, fibrosis and/or proteinuria) [23,40]. Recent studies have supported these findings. Induction of diabetes in rats genetically deficient in ETB causes severe hypertension and progressive renal failure [41]. In a mouse model of polycystic kidney disease, ETB, but not ETA, antagonism accelerated the cystic kidney disease [42]; notably, the ETB blocker effect was prevented by ETA antagonism. In high dietary protein-induced CKD in rats with reduced renal mass, ETA, but not combined ETA/B antagonism, prevented the reduction in GFR [29]. In a rat model of high AII hypertensive renal injury, ETA blockade reduced glomerular injury to a greater extent than did combined ETA/B antagonism [43]. All of these findings are in keeping with the known effect of ETA, but not ETB, to mediate vasoconstriction, cell injury and fibrosis in the kidney [22]. Thus, the available data support using ETA-selective antagonists in CKD. Having said that, it must be recognized that most of the studies are in experimental animals; until ETA-selective and combined ETA/B antagonists are compared in patients with CKD, this issue remains unresolved. Nonetheless, my own bias is that, at least in initial studies on CKD progression, ETA-selective blockers should be used.

Conclusion

In summary, ET-1 is an important pathogenic factor in hypertension, particularly in association with metabolic syndrome and/or atherosclerosis. In addition, ET-1 plays a substantial role in CKD progression. Numerous pre-clinical, as well the few completed clinical, studies suggest a substantial beneficial role for ET receptor antagonists, and particularly ETA blockers, in these disorders. However, in order to move forward, several key issues need to be addressed. First, the nature and mechanisms of ET antagonist-related adverse effects need elucidation. Second, appropriate doses of ET blockers need to be defined, including determination of ones that are truly ETA-selective. Third, consideration must be given to which agents would best be co-administered with ET blockers. Finally,

given the great promise of these drugs, the pharmaceutical industry and academia must work together to conduct long-term studies on cardiovascular and renal outcomes.

Acknowledgments

The research from the author's laboratory was supported in part by NIH grant DK96392.

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Figure 1.

Regulation of ET-1 production in the vasculature and the kidney. IL-1 – interleukin-1, LDL – low density lipoproteins, PDGF – platelet derived growth factor, ROS – reactive oxygen species, TGF – transforming growth factor. TNF – tumor necrosis factor, TxA2 – thromboxane A2.

Figure 2.

Effect of ET-1 on vascular and renal cells, resulting in hypertension, atherosclerosis and chronic kidney disease (CKD). While ETA likely mediates most of these effects of ET-1, vascular smooth muscle ETB can mediate vasoconstriction. ECM – extracellular matrix, ETA – ETA receptor, ROS – reactive oxygen species.