Endothelin antagonism for patients with chronic kidney disease: still a hope for the future

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ABSTRACT

Endothelin is tightly involved in the regulation of vascular and renal function in health and in disease. In a variety of animal models of kidney disease, endothelin promotes renal injury through effects on inflammation and fibrosis. Furthermore, experimental data strongly suggest that blocking the actions of endothelin should be beneficial in patients with chronic kidney disease. However, despite encouraging pre-clinical and clinical evidence, endothelin antagonists are not yet an established treatment option in patients with chronic kidney disease. This article reviews key physiological and pathophysiological aspects of the endothelin systems as relevant for CKD, as well as results of pre-clinical and clinical studies on the use of endothelin antagonists in CKD. We will also provide an outlook on the future of endothelin antagonism in CKD, and issues to be resolved before endothelin antagonists are to become a reality for patients with CKD.

INTRODUCTION

More than 20 years ago, Yanagisawa et al. [1] discovered endothelin, the most powerful vasoconstrictor substance known in humans. In addition to its role in cardiovascular biology, the involvement of endothelin in many other physiological systems, which, to name a few, includes the nervous, the immune and the reproductive systems, has been firmly established. Endothelin is also involved in regulating the structure and function of the kidney, and experimental data strongly suggest that blocking the actions of endothelin might be beneficial in patients with chronic kidney disease (CKD). However, despite encouraging pre-clinical and clinical evidence, endothelin antagonists are not yet an established treatment option in patients with CKD. So far, approved clinical indications for endothelin antagonists are only pulmonary arterial hypertension and scleroderma-related digital ulcers. This article reviews key physiological and pathophysiological aspects of the endothelin systems as relevant for CKD, as well as results of pre-clinical and clinical studies on the use of endothelin antagonists in CKD. We will also provide an outlook on the future of endothelin antagonism in CKD, and issues to be resolved before endothelin antagonists are to become a reality for patients with CKD.

PHYSIOLOGY OF THE VASCULAR ENDOTHELIN SYSTEM

Encoded by separate genes, the human endothelin family encompasses three 21-amino-acid long isopeptides, endothelin-1, endothelin-2 and endothelin-3 (ET-1, ET-2 and ET-3) [2]. In the cardiovascular and renal systems, the most extensively studied and most important isoform is ET-1. Endothelial cells are the major source of ET-1 in the vasculature (Figure 1). There are two types of receptors for endothelins: the endothelin type A (ETₐ) and the endothelin type B (ET₇) receptor. Both ETₐ and ET₇ receptors, located on vascular smooth muscle cells, mediate strong and long-lasting vasoconstrictor responses to ET-1. The ET₇ receptor, however, has two additional functions that tend to oppose the vasoconstrictor effects of ET-1. Activation of ET₇ receptors on endothelial cells causes release of prostaglandins and nitric oxide, resulting in relaxation of the underlying smooth muscle cells. Further, endothelial ET₇ receptors are important for clearing ET-1 from the circulation, thus limiting the vasoconstrictor activity of ET-1 (for a detailed discussion of the various roles of the ETₐ and ET₇ receptors, please see review [3]). In mice, endothelial-cell-specific disruption of the ET-1 gene reduces blood pressure (BP), providing genetic evidence for an essential role of endothelium-derived ET-1 in the maintenance of basal vascular tone and BP, with an overall BP-increasing effect [4]. This is also the case in humans, as the overall effect of ET-1
generated in the human vasculature is vasoconstriction [5]. In addition to the regulation of vascular tone, ET-1 also has growth-promoting effects on vascular smooth muscle cells.

PHYSIOLOGY OF THE RENAL ENDOTHELIN SYSTEM

In the kidney, the inner renal medulla, and in particular the principal cells of the inner medullary collecting duct (IMCD), produces the greatest amounts of ET-1 (Figure 2). Both ET_A and ET_B receptors are expressed in this region [6, 7]. Collecting duct cells express ET_A and ET_B receptors, pericytes of the vasa recta and smooth muscle cells of the more upstream afferent arterioles ET_A and ET_B receptors [8], and endothelial cells of the vasa recta and afferent arterioles ET_B receptors. Mice with collecting duct-specific deletion of ET-1 were found to have salt-sensitive hypertension, demonstrating the importance of ET-1 within this particular nephron segment for fluid balance and BP control [9, 10]. A further series of experiments with cell-specific deletions of the receptors showed that it is mainly the ET_B receptor on collecting duct cells that, in an autocrine fashion, mediates the natriuretic and antihypertensive effects of renal medullary ET-1. Nephron-specific deletion of ET_A receptors in mice causes mild volume expansion under a high salt intake without a change of BP [18]. In female rats, ET_A receptors within the renal medulla contribute to ET-1-induced natriuresis by a nitric oxide synthase 1 (nNOS)-dependent mechanism, an effect that is abolished by ovariectomy [19]. Finally, there is recent evidence that ET-1 inhibits sodium reabsorption through both ET_A and ET_B receptors in the cortical collecting duct [20]. Therefore, summarizing the experimental data on the roles of the renal ET_A and ET_B receptors for renal sodium excretion, the activation of renal ET_B receptors clearly favours sodium excretion and thus contributes to a lower BP. The role of renal ET_A receptor is less clear, but recent experimental evidence suggests that the activation of those receptors may as well favour natriuresis, at least under specific circumstances.

PATHOPHYSIOLOGY OF THE ENDOTHELIN SYSTEM IN CKD

Alterations in the function and structure of mesangial cells and podocytes play an important pathogenetic role in the progression of renal diseases. Human mesangial cells and podocytes express functionally active endothelin receptors as they bind ET-1, which subsequently causes a rapid increase in intracellular calcium levels [21]. Thus, ET-1 significantly affects signal transduction and proliferation of mesangial cells and podocytes. There is also strong evidence that the activation of the endothelin system directly promotes renal fibrosis, as rats with transgenic overexpression of ET-1 develop severe glomerulosclerosis and interstitial fibrosis [22]. Cell culture studies have further shown that exposure to protein overload, as a general model of proteinuric nephropathies, and exposure to shigatoxin, as a model for the haemolytic uraemic syndrome, both upregulate ET-1 expression in cultured podocytes [23, 24]. The release of ET-1 then results in further deterioration of podocyte structure and function by an autocrine mechanism [23]. Experimental evidence for involvement of the endothelin system is particularly strong in diabetic kidney disease, as ET-1, the ET_A and ET_B receptors are strongly overexpressed in the renal cortex of rats with streptozotocin-induced diabetes [25].

In humans, there are only few data on the expression of the components of the endothelin system in patients with
kidney disease. For example, an increased expression of ET-1 has been found in kidneys of patients with IgA nephropathy [26, 27]. Some studies further suggest that urinary ET-1 levels may be a useful marker of renal injury [28, 29]. There is also some evidence from human studies that the ETA receptor, and perhaps also the activation of the ETB receptor, contribute to the progression of atherosclerosis, which is a significant clinical complication of CKD [30, 31].

**EXPERIMENTAL STUDIES WITH ENDOTHELIN ANTAGONISTS**

There is abundant evidence from experimental studies for the beneficial effects of endothelin antagonism in non-diabetic and diabetic models of renal disease. Ortmann et al. [32] have shown that 4-week oral treatment with the ETA receptor selective antagonist darusentan partially reverses ageing-associated glomerulosclerosis in rats. Further experiments from that study demonstrated that the structural damage to podocytes induced by puromycin aminonucleoside, as a model of focal segmental glomerulosclerosis, is attenuated by ETA Receptor, but not ETB receptor, blockade [32]. In the shigatoxin-induced model of the haemolytic uremic syndrome, ETA receptor blockade was able to prevent the pathological changes of the podocyte cytoskeleton [24]. Together, these studies support the concept that the activation of the endothelin system can contribute to renal disease progression, mediated partly via actions on podocytes.

Experimental data on whether selective ETA receptor blockade should be preferred over non-selective ETA/ETB receptor blockade for preventing progressive renal disease are not entirely consistent. In models of non-diabetic renal disease, some studies, such as in the ageing-associated glomerulosclerosis model, suggest that ETA selective blockade is more effective than non-selective ETA/ETB receptor blockade, whereas others, such as studies in the renal mass reduction model, suggest that treatment with both types of blockers are equally effective in protecting from disease progression [33, 34].

In the streptozotocin model of diabetes, selective ETA receptor blockade has been shown to reduce albuminuria, extracellular matrix production and glomerular inflammation [35, 36]. Further studies have shown that selective ETA receptor and non-selective ETA/ETB receptor blockade both reduce albuminuria and glomerular permeability, but only selective ETA receptor blockade reduces glomerular inflammation [37]. Thus, selective ETA receptor blockade may be preferable for treatment of diabetic kidney disease. Of note, in uninephrectomized rats with streptozotocin-induced diabetes, regression of glomerular and interstitial injury was achieved by ETA receptor blockade with avosentan combined with renin–angiotensin system inhibition with lisinopril, whereas each drug alone was only able to attenuate glomerular and interstitial injury, suggesting synergistic effects of combining the two treatment principles [38]. Chronic ETA receptor blockade has further been shown to normalize endothelial function and reduce atheroma formation in a mouse model of atherosclerosis, which, as alluded to earlier, presents a significant comorbidity in CKD [39].

**CLINICAL STUDIES WITH ENDOTHELIN ANTAGONISTS**

There was some evidence from early clinical experimental studies that the contribution of endothelins to vascular tone of the forearm vasculature is reduced (rather than increased) in patients with advanced CKD compared with healthy controls [40, 41]. Nonetheless, Goddard et al. [42] demonstrated that the ETA selective antagonist BQ-123 significantly reduces BP and increases renal blood flow in hypertensive patients with non-diabetic CKD. In the same study, combined ETA/ETB receptor blockade also reduced BP, but was not able to increase renal blood flow. The renal haemodynamic effects of selective ETA receptor blockade were similar to those commonly associated with renin–angiotensin system inhibition in that a reduction of filtration fraction was observed, perhaps suggesting similar renal protection in the long term [42]. Subsequent studies showed that ETA receptor blockade with i.v. BQ-123 combined with renin–angiotensin system inhibition even had synergistic renal haemodynamic effects and together were able to increase sodium excretion significantly [43]. These synergistic effects were abolished with ETB receptor blockade or with nNOS inhibition, suggesting that the beneficial effects of ETA blockade were mediated via activation of the ETB receptor. By way of mechanism, blockade of the ETA receptor appears to leave more ET-1 available for activation of the ETB receptor, i.e. ET-1 is shifted to activate more ETB receptors [43]. Further, studies by Dhaun et al. [44] demonstrated that acute ETA receptor blockade with i.v. BQ-123 reduces BP, arterial stiffness and proteinuria in patients with non-diabetic kidney disease. While the reduction in BP and the increase in renal blood flow were similar to the calcium channel blocker nifedipine—as a control—in comparison with BQ-123, there was a substantially greater reduction in arterial stiffness and proteinuria with BQ-123, suggesting BP-independent effects of ETA receptor blockade.

In line with these acute effects ETA receptor blockade, 6 weeks oral treatment with the sulphonamide-based, highly ETA receptor selective antagonist sitaxentan reduced proteinuria more than oral treatment with nifedipine, despite similar reductions in BP [45]. Only sitaxentan reduced filtration fraction, suggesting that the disparate effects on proteinuria may at least in part be explained by differences in the renal haemodynamic effects of these two drugs. Interestingly, no cases of clinically significant oedema were reported with sitaxentan, which is highly selective for the ETA receptor (>1000:1 ETA:ETB binding selectivity). Sitaxentan was approved for the treatment of pulmonary arterial hypertension in 2006. Increases in liver enzymes are relatively common with this and other endothelin antagonists (up to ≥10% of patients [46]). Unfortunately, several cases of fatal liver failure were reported with sitaxentan in the following years, and the drug was withdrawn from the market in 2010. It has been postulated that some endothelin antagonists, in particular bosentan and sitaxentan [47], cause hepatitis by inhibition of bile salt transporter pumps, but immune-mediated or idiosyncratic mechanisms are also possible.

Clinical trials in patients with type 2 diabetes and nephropathy have also been conducted with avosentan, a
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**REFERENCES**

3. Schneider MP, Boesen EI, Pollock DM. Contrasting actions of endothelin antagonists together with adequate use of diuretics may also help to overcome oedematous side effects in CKD patients. In terms of liver toxicity, inhibition of hepatobiliary transporters appears to differ significantly between specific endothelin antagonists, and we clearly need to learn more about the precise molecular mechanisms [47]. Of note, endothelin antagonists are teratogenic and will not be an option for women of childbearing potential [52].

In summary, endothelin antagonists have demonstrated impressive antiproteinuric effects in CKD patients, even in those with inhibition of the renin–angiotensin system. Since renin–angiotensin system inhibition can only provide partial protection from renal disease progression, further development of endothelin antagonists for patients with kidney disease still remains a hope for the future.

**ACKNOWLEDGEMENT**

J.F.M. is supported by the European Commission (Grant 241544, SysKid).

**CONFLICT OF INTEREST STATEMENT**

J.F.M. reports consultant honoraria from Abbott, Acetion and Novartis.

Received for publication: 8.4.2013; Accepted in revised form: 8.7.2013