

*Short Editorial Review***Endothelin in renal disease: role of endothelin antagonists**

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In spite of tremendous progress in the understanding of human disease, the search for new mediators continues as numerous conditions remain poorly understood. In particular in many forms of renal disease, effective and cause-orientated forms of therapy are still lacking. The discovery of new pathogenetic mechanisms often leads to the development of new drugs with previously unknown properties which may offer new treatment modalities. Endothelin is a recently discovered potent biological mediator which exists in three closely related isoforms (i.e. endothelin-1, -2 and -3 [1–3]). Endothelins belong to a family of 21 amino acid peptides with two disulphide bridges [1,3]. The main vascular effects of endothelin are transient vasodilatation and profound and sustained vasoconstriction [4]. Endothelin also exerts marked renal effects, acts as a mitogen and stimulates proliferation of vascular smooth muscle and glomerular mesangial cells [5–7].

Important sources of the peptides are endothelial cells, neurons, renal cells and at least under certain conditions also vascular smooth muscle cells. Stimuli for the release of endothelins include hypoxia and/or ischaemia [8], but also humoral factors (angiotensin II, vasopressin, transforming growth factor-beta, insulin, thrombin and several cytokines) and potentially nephrotoxic drugs such as radiocontrast agents, cyclosporin, amphotericin B and OKT-3 [1,3,9,10–22]. On the other hand, nitric oxide and atrial natriuretic peptide inhibit endothelin production via a cyclic GMP-dependent mechanism [1,3,11,20]. In addition, smooth muscle cells appear to release an inhibitory factor which limits the production of the peptide. This may explain why intact tissues such as the blood vessel wall produce markedly less endothelin than isolated cells in culture. *In vivo* in humans, endothelin plasma levels are very low [21]. However, in different disease states, elevated endothelin plasma levels have been described (see below, Table 1).

In the kidney, endothelin reduces renal blood flow and glomerular filtration rate [10,22–25]; this is mainly due to vasoconstriction of both afferent and efferent arterioles. Systemic infusion of endothelin-1 in humans *in vivo* leads to blood pressure increase, sodium reten-

tion and reduction in urine flow [24,25]. Although *in vitro* endothelin inhibits renin release [23,26], in the intact organism renin plasma levels do not change or increase (due to renal vasoconstriction) after infusion of endothelin-1 [25]. Endothelin stimulates release of aldosterone, vasopressin and atrial natriuretic peptide under experimental conditions [9,10]. However, *in vivo* in humans, it does not influence the plasma levels of these hormones [24]. The role of the mitogenic properties of endothelin [5–7] in the kidney is still unclear, but it could be involved in proliferative glomerular diseases.

Endothelins exert their biological effects via activation of specific receptors. These membrane-bound receptors have seven transmembrane domains and are coupled to G-proteins; three types of endothelin receptors have been cloned, i.e. ET_A, ET_B and ET_C receptors [27]. Endothelin-1, the primary product of endothelial cells, preferentially activates ET_A receptors. ET_B receptors exert no isoform specificity and are equally activated by all endothelin isoforms, while the ET_C receptor preferentially binds endothelin-3 [28]. ET_A receptors on vascular smooth muscle cause vasoconstriction and mediate proliferation, although ET_B receptors contribute to these effects. Endothelial cells express only ET_B receptors linked to nitric oxide and prostacyclin formation. The endothelin receptors on renal cells have only partially been characterized. However, the ET_A receptors seem to be expressed mainly in the glomerulus, the vasa recta bundle and the arcuate artery, while the ET_B receptor predominates in the initial and terminal

Table 1. Possible role of endothelin in disease

Heart disease	Myocardial infarction Coronary spasm Cardiac shock Heart failure
Vascular disease	Atherosclerosis Takayashu's disease Raynaud's disease
Hypertension	Arterial hypertension (?) High altitude pulmonary hypertension
Other	Migraine Subarachnoid haemorrhage Renal failure Hepatorenal syndrome Low tension glaucoma

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inner medullary collecting duct and also in the glomerulus [29].

Recently, new molecules have been synthesized, which *in vitro* inhibit the effects of endothelin (Table 2) [30–34]. Certain of these molecules inhibit ET_A receptors only, while others interfere with both ET_A and ET_B receptors. As both ET_A and ET_B receptors are expressed on vascular smooth muscle also in the human [35–37], combined antagonists more effectively interfere with the vasoconstrictor effects of endothelin. On the other hand, non-selective endothelin antagonists also reduce the release of nitric oxide and prostacyclin from the endothelium and hence the potentially beneficial vasodilator effects of endothelin. In the human skin microcirculation *in vivo*, both combined and selective endothelin antagonists potently inhibit the vasoconstrictor effects of endothelin-1 [38]. In the kidney, it appears that both receptors contribute to the effects of endothelin. However, although both ET_A and ET_B receptors are present, their distribution in the kidney is not uniform suggesting different function [29]. Hence, it is likely that combined endothelin antagonists are required to interfere with the renal effects of endothelin.

Several experimental studies suggest a pathophysiological role of endothelin in renal failure. Indeed, acute ischaemic renal failure leads to an increase in endothelin release and/or endothelin receptor upregulation [39–42]; this effect can be reversed by endothelin receptor antagonists or drugs blocking the endothelin converting enzyme [43–45]. In uraemic patients, endothelin plasma levels are elevated [46]. In particular, renal failure induced by nephrotoxic agents seems to be related to increased endothelin levels; this is true for radiocontrast agents independent of their type [47–50], as well as for other potentially nephrotoxic drugs, like amphotericin B [51] and possibly cisplatin [52]. Immunosuppressive agents such as cyclosporin and FK 506 also modulate endothelin release (see below). Obviously, acute renal failure can be caused by a variety of stimuli and the importance of a given mediator may vary depending on the major cause involved. Ischaemic renal failure is relatively well defined experimentally and is particularly suitable for studies with newly developed drugs. Indeed, in a monkey model, decreases in renal blood flow in acute ischaemic renal failure could be prevented by an ET_A/ET_B receptor antagonist [53].

Table 2. Endothelin antagonists

Drug	Receptor
BE-18257A/B	ET _A
BQ-162	ET _A
BQ-123	ET _A
BQ-153	ET _A
PD 147953 (=FR 139317)	ET _A
RO-462005	ET _A /ET _B
PD 142893	ET _A /ET _B
PD 145065	ET _A /ET _B

In chronic renal failure, only very few studies exist; they all found increases in endothelin plasma levels and/or gene expression [54,55]. The mechanisms involved are not entirely clear. Endothelin levels could be increased because of (1) a reduced renal clearance, (2) loss of inhibitory mechanisms in renal failure or (3) due to stimulatory effects, i.e. of uraemic toxins. In patients with renal failure an endogenous inhibitor of the l-arginine/nitric oxide pathway (i.e. dimethylarginine or ADMA [55] accumulates. The inhibition of nitric oxide production could explain an increased endothelin production as nitric oxide reduces endothelin production from the blood vessel wall via a cGMP-dependent mechanism [11]. Patients on haemodialysis also have elevated plasma endothelin levels [46]. The volume contraction after haemodialysis seems to increase plasma levels of endothelin further, possibly through an activation of the sympathetic nervous system [46,57,58], which is known to increase plasma endothelin levels [59,60]. This may explain the differences observed between peritoneal dialysis (CAPD) and no dialysis on the one hand and haemodialysis on the other, although this is controversial [46,58]. High-flux membranes (PAN, PMMA, CTA) seem to clear endothelin better than normal membranes [61]. Whether these findings reflect a pathogenetic role for endothelin in chronic renal disease in humans will be clarified by appropriate clinical studies with endothelin antagonists in the future.

In disease states with secondary involvement of the kidney—like diabetes [62], hepatorenal syndrome [63], thrombotic thrombopenic purpura [64], septic shock [65,66], but also in congestive heart failure [67–70] and severe atherosclerosis [71]—elevated plasma levels of endothelin have been described and may contribute to the deterioration of renal function occurring under these conditions. Ongoing experimental and clinical trials with endothelin antagonists will elucidate the pathogenic role of endothelins in these disease states and its involvement in renal functional impairment in particular. Similarly, in autoimmune diseases like Morbus Wegener and Morbus Raynaud [59], elevated endothelin plasma levels occur. In a mice lupus nephritis model, endothelin gene expression is increased and tends to normalize with prednisolone therapy [72]. It is conceivable, therefore, that inflammatory diseases of the vascular wall or the glomerulus are associated with an activation of the endothelin axis. Whether or not such an activation is primary or secondary in nature in these diseases requires experimental and later clinical studies with specific endothelin receptor antagonists.

The role of endothelin in arterial hypertension is controversial (see [2,73]). Infusion of endothelin does increase blood pressure in experimental animals and in humans [10,74]. Moreover, patients with endothelin-secreting haemangioendotheliomas are hypertensive [75]. Whether or not endothelin production is altered in hypertension is uncertain. Although some studies found increased plasma levels of endothelin, many other studies found no differences as compared to

controls. However, circulating endothelin may not reflect local levels of the peptide, as in the blood vessel wall endothelin is primarily released abluminally [76]. Indeed, in DOCA-salt hypertension vascular endothelin production is increased in the presence of normal plasma levels of the peptide [77]. In the SHR, however, both circulating and vascular endothelin is suppressed. Similarly, in the renal medulla of the SHR, the endothelin content is reduced [78]. These experimental findings suggest that endothelin may be differently involved in different forms of hypertension, possibly also in the human. To further elucidate the role of endothelin, transgenic and gene knockout rats have been produced. Endothelin-2 transgenic rats are normotensive (possibly because of the activation of compensatory vasodilator mechanisms) and endothelin-1 gene knock-out mice are actually hypertensive [79]. For the interpretation of the data derived from the latter models, one has to be reminded of the fact that in humans increased endothelin levels, for instance derived from vascular tumours, do indeed cause hypertension. Moreover, in the human hand vein circulation of patients with essential hypertension, the vasoconstrictor response to endothelin is increased. Finally, endothelin antagonists lower blood pressure in salt-depleted monkeys in the SHR and DOCA-salt hypertensive rats. The surprising finding that endothelin knock-out rats have profound malformations of the throat indicates that the peptide may be importantly involved in the development of these organs [79].

Cyclosporin therapy is established in the treatment of host versus graft rejection. However, the drug often leads to hypertension and impairs renal function. In cultured endothelial cells cyclosporin stimulates endothelin production [80,81]. Furthermore, in the renal medulla of rats [82] and rabbits [83], cyclosporin, and even more so its metabolites [83], but also FK 506 [84], stimulate the production of endothelin, inhibit prostacyclin release and in turn lead to renal vasoconstriction, especially in the afferent arteriole [85]. In addition, both cyclosporin and FK 506 have cytotoxic effects in renal cells [84]. In transplant recipients, cyclosporin increases endothelin levels [86]. In the rat renal circulation, cyclosporin reduces renal blood flow; this effect can be prevented or reversed by endothelin antibodies or endothelin antagonists [87]. However, whether inhibition of endothelin can prevent cyclosporin-induced side effects, especially nephrotoxicity and hypertension, has still to be established.

Hence, in summary, the endothelins are a new and potentially very important family of peptides with potent effects in the cardiovascular system and the kidney in particular. Their biological effects could explain a variety of disturbances occurring in renal disease and in several forms of hypertension. Of great interest for renal physiologists and nephrologists is the fact that the endothelin system is activated in several renal diseases and that endothelin antagonists are effective in reversing impaired renal function in experimental models. Definitive proof for an involvement of endothelins in renal function and disease in humans

awaits the results of ongoing clinical trials with new and specific endothelin receptor antagonists.

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