The clinical role of endothelin antagonists

During the ‘Kongref für Nephrologie 2000’ (2–5 September 2000, Vienna, Austria) a pre-congressional symposium was held. The first speaker was Ariela Benigni from Bergamo, Italy. As she said, exogenous endothelin 1 (Et-1) infusion reduces the renal plasma flow (RPF) by approximately 25% at doses which do not alter systemic blood pressure (MAP). The effect of Et-1 on RPF is mediated by constriction of afferent and efferent glomerular arterioles. Furthermore, Et-1 at these doses decreases kT and GFR. Additional effects are tubular reduction of Na reabsorption, mesangial cell proliferation and increased synthesis of mesangial matrix. The effects are mediated by differentiated expression of ET receptors (Et-R): while the Et-A-R resides primarily on afferent and efferent arterioles and on mesangial cells, Et-B-R will be found in the medulla and the vasa recta bundles; in addition Et-B-R occur on glomerular endothelial cells. Ariela Benigni postulated a role for Et in the following two conditions: i) Cyclosporine toxicity; ii) Chronic progressive nephropathies.

In a model of subtotal nephrectomy in the rat, proteinuria increased 7-fold within the first 120 days, and this was paralleled by a similar increase of urinary Et-1 excretion and a dramatic increase in the expression of the Et-B-R. An enhancement of urinary Et-1 excretion and/or renal Et-1 synthesis has also been shown in passive Heyman nephritis, STZ diabetes, chronic glomerulonephritis (CGN) in humans, SLE-nephritis, kidney transplantation, unilateral nephrectomy, NIDDM with albuminuria, and cyclosporine A nephrotoxicity. In CGN, enhanced transcription of the genes for Et-1, Et-A-R, Et-B-R and ECE-1-alpha (endothelin converting enzyme) have all been demonstrated. One possible mechanism of these changes is proteinuria according to Dr Benigni. It has also been shown some time ago that albumin (10 mg/ml) as well as IgG increase Et-1 secretion 2- to 3-fold if these proteins are added to proximal tubular cells in culture. Approximately 75% of this Et-1 is secreted basolaterally, where proximal tubular cells in vivo abut against interstitial cells. The latter show high affinity binding of Et-1. In response to stimulation by Et-1 they exhibit proliferation as well as upregulation of their collagen α-1 gene expression. Endothelin receptor antagonists have now been found to reduce proteinuria and to slow the progression of renal insufficiency in a number of animal models.

T. Rabelink, Utrecht, The Netherlands, showed observations of the haemodynamic effects of Et-antagonists in healthy volunteers. He observed an effect of BQ 123, an Et-A-R specific antagonist, to cause an increase in blood flow (forearm perfusion studies). BQ 788—a selective endothelin-B-R antagonist—caused a 30% decrease of blood flow. In the kidney, Dr. Rabelink observed similar though quantitatively larger effects in patients with renal diseases. According to Dr Rabelink, Et-1 has other important effects on the vascular wall. For instance, it stimulates the production of TNF-α, INF-γ, and TGF-β in tissue macrophages. Also, Et-1 enhances antigen presentation by macrophages to T-cells. Et-1 stimulates smooth muscle cells to proliferate and it contributes to interstitial fibrosis. Dr Rabelink showed studies of leucocyte/endothelial interaction under flow conditions. In these studies leucocytes were 4-fold more adherent to endothelium if the latter had previously been treated with Et-1. Dr Rabelink also presented clinical data from eight diabetic patients with albuminuria who received 6 weeks of treatment with ABT 627, a selective Et-A-R antagonist. The study was performed in a double blind, cross-over, placebo-controlled, prospective manner. ABT 627 caused a significant reduction of the MAP and it reduced albumin excretion rate by approximately 70%. There was, however, a tendency towards fluid retention and several patients complained of headaches during treatment by endothelin antagonist.

Astrid Seeber, Stockholm, Sweden, measured venous plasma levels of Et in haemodialysis (HD) patients and healthy controls. In HD patients, Et-1 concentrations were increased 4-fold; big-Et-1 levels were increased even more (10-fold). Additional studies of the plasma half-life of exogenously infused Et-1 and big-Et-1 indicated a prolongation in HD patients by 200% for Et-1 and by 120% for big-Et-1. Thus, the observed increases of Et plasma levels in uraemia were explained—at least in part—by a decreased metabolic clearance rate. Further studies in HD patients using exogenous infusions of Et-1 and of big-Et-1 elicited vasoactive responses that were at control level (changes of MAP, heart rate, organ perfusion); in other words, uraemia did not seem to interfere with an unremarkable response to exogenous Et. Dr Seeberger also measured plasma concentrations of Et during hypotension in HD patients. No differences were detectable between hypotension prone and blood pressure stable HD patients.

E. Büssemaker, Frankfurt/Dresden, FRG, presented new data on the functional role of Et-1 in uraemic patients (forearm perfusion studies; FBF). He tested
normotensive HD patients and healthy controls. As described he found elevated concentrations of Et-1 in peripheral venous plasma in his patients. However, surprisingly the response in HD patients to BQ 123 as well as to BQ 123 plus BQ 788 was clearly and significantly less than in healthy controls. He also tested the response to exogenous infusion of Et-1. Again, unexpectedly he observed a left shift of the dose response curve indicating a significantly increased vascular sensitivity of uraemic patients to Et-1. As an explanation for his perplexing findings he postulated that endothelial secretion of Et-1 in uraemia was reduced and that Et-receptors were normal. He went on to suggest that the elevated plasma concentrations of Et were probably caused by the decreased metabolic clearance of Et in uraemia. Obviously, this interesting hypothesis will need further confirmation.

C. Braun, Mannheim, FRG, has studied ‘chronic rejection’ (Fischer to Lewis model of experimental transplantation). In this model Et excretion, renal Et content and renal Et-1 mRNA expression all increased significantly after transplantation, as did proteinuria and blood pressure. The increased Et was localized in the endothelium and the smooth muscle cells of large intrarenal blood vessels. Rats developed glomerulosclerosis, vascular damage and increased MHC-II expression in this model. Chronic treatment with an Et-A-R antagonist (LU 135252) improved creatinine clearance, scores of glomerular damage and survival in these rats. It remains unclear, however, whether this interesting model conforms to chronic allograft rejection in humans—or whether it is more typically a model of transplant arteriosclerosis.

Taken together, the symposium outlined avenues of future research and application of endothelin antagonists in kidney diseases. As outlined by M. Kirchengast in his final comment, enormous clinical progress has been achieved with these compounds in cardiology. It is therefore expected that the endothelin antagonists will soon be licensed for these purposes.

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