Treatment of cardiovascular changes in renal failure—ACE inhibition, endothelin receptor blockade or a combination of both strategies?

K. Amann¹, K. Münter², J. Wagner³, V. Balajew¹, S. Hergenröder⁴, G. Mall³ and E. Ritz²

¹Department of Pathology and ²Department of Internal Medicine, University of Heidelberg, ³Department of Pathology, University of Darmstadt and ⁴Knoll AG, Ludwigshafen, Germany

Background

Cardiovascular complications are a major problem in patients with renal failure, and cardiac death is the leading cause of death in these patients. Clinical and experimental data have documented a pathogenetic role for the local renin–angiotensin system.

Recently, a potential role for endothelin-1 (ET-1) in the development of cardiovascular changes in renal failure was also postulated, i.e. increased ET-1 mRNA and protein excretion were found in the heart of uremic patients and of subtotally nephrectomized rats with chronic renal failure. In addition, a close correlation between thickening of the wall of elastic arteries and plasma ET-1 was documented in uremic patients. Thus, treatment with angiotensin-converting enzyme inhibitors (ACE-I), specific or unspecific ET-1 receptor blockers or a combination of both drugs seem to be promising therapeutic approaches. Recently, experimental studies in various models of renal damage pointed towards an additional beneficial effect of a combination therapy of ACE-I and ET blockade compared with the respective monotherapies.

The aim of the present study was to investigate the effect of treatments with both monotherapies and a combination therapy on the development of cardiovascular structural changes in an experimental model of renal failure.

Materials and methods

At 24 h after subtotally nephrectomy (SNX), male Sprague-Dawley rats (200 g) were left untreated or started on treatment with the selective ET₄ receptor antagonist LU 135252 (20 mg/kg/day), the ACE-I trandolapril (0.3 mg/kg/day) or a combination of both therapies. The animals were compared with sham-operated control rats (sham) and followed for 15 weeks. Blood pressure was monitored by telemetry in several animals per group during the experiment. Left ventricular weight (LVW), volume density of cardiac interstitial tissue, volume density and length density of myocardial capillaries, and wall thickness of intramyocardial arteries and of the aorta were analysed by morphometry.

Results

Mean arterial blood pressure was significantly greater in untreated SNX (136 ± 0.76) than in sham-treated (105 ± 0.52) and all treated SNX groups. It was lowest in the combination therapy group. Serum creatinine (75 ± 5.9 μmol/l) and proteinuria (235 ± 93 mg/kg/day) were significantly increased after SNX and were lower with ACE-I (60 ± 2.74 μmol/l and 118 ± 46 mg/kg/day, respectively) than with ET receptor blockade (90 ± 23 μmol/l and 216 ± 112 mg/kg/day, respectively). In untreated SNX animals, a significant increase in relative LVW (2.27 ± 0.15 vs 1.5 ± 0.12 g), cardiac interstitial tissue (3.12 ± 0.63 vs 2.08 ± 0.57%), wall thickness of intramyocardial arteries (5.52 ± 1.69 vs 3.79 ± 0.67 μm) and of the aorta (0.68 ± 0.11 vs 0.52 ± 0.05 mm²) was seen compared with sham-operated control rats.

These structural changes were completely and comparably prevented by all three treatments. In contrast, the decrease in myocardial capillary supply after SNX (3307 ± 534 vs 3995 ± 471 mm/mm²) was only completely prevented by the ET-1 receptor blocker.

Summary and conclusion

ACE-I and specific ET₄ receptor blockade comparably prevented the development of structural cardiovascular alterations such as LVH, myocardial interstitial expansion and wall thickening of intramyocardial and extracardiac arteries in experimental renal failure. However, the decrease in myocardial capillary supply and the concomitant increase in intercapillary distance could only be prevented by ET₄ receptor antagonism. These capillary changes which have been shown to occur in experimental renal failure as well as in uremic patients play an important role in the pathogenesis of reduced cardiac ischaemia tolerance in renal failure.

The data argue for a potential role of the local renin–angiotensin system as well as of the ET system in the pathogenesis of cardiovascular changes in renal failure and for ET receptor blockade as a new therapeutic option in the treatment of these alterations.
In particular, myocardial capillary supply, which is particularly important for ischaemia tolerance in renal failure, seems to be modulated and regulated predominantly by ET-1. In contrast to what was found with respect to structural and functional changes of the kidney in various experimental models of renal damage, a combination therapy—at least in the doses used—does not seem to provide additional benefit in the prevention of cardiovascular changes compared with the respective monotherapies.

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Role of sympathetic nerves in the differential effects of T-type and L-type calcium channel blockers on renin secretion and renin gene expression

M. Hinder1, C. Wagner2, B. K. Krämer3 and A. Kurtz2

1Hoffmann-La Roche AG, Emil-Barell-Str. 1, 79630 Grenzach-Wyhlen, 2Institute of Physiology and 3Klinik und Poliklinik für Innere Medizin II, University of Regensburg, D-93053 Regensburg, Germany

Introduction

One major side effect of calcium channel blockers (CCBs) is the stimulation of the renin system [1,2] which, at least in part, counteracts the desired effects of treatment with CCBs. The mechanisms underlying the stimulation of the renin system are probably multifactorial and are not completely understood. They involve systemic effects, such as the fall in blood pressure and activation of sympathetic outflow, and direct effects on the level of renin-secreting juxtaglomerular cells. Classical CCBs act primarily on L-type (long-lasting, high voltage-activated) calcium channels, whereas mibefradil selectively blocks T-type (transient, low voltage-activated) over L-type calcium channels [3,4]. Wagner and co-workers previously have shown that this pharmacological difference seems to translate into different effects in vivo. They could demonstrate that the T-type CCB mibefradil and the L-type CCB amlodipine have opposite effects on renin secretion and renin gene expression [5]. In the present investigation, we aimed to investigate the role of renal sympathetic nerves in the differential effects of T- and L-type CCB on renin secretion and gene expression.

Parameters assessed

Systolic blood pressure was measured by the tail cuff method. Plasma renin activity (PRA) was determined by using a commercially available radioimmunoassay. Renin gene expression was determined as the ratio of renin mRNA to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA. Renin and GAPDH mRNA in the kidneys were measured by RNase protection, as described previously [5].

Statistics

Results are expressed as mean ± SEM and were compared using Student’s t-test. Differences were considered to be statistically significant when P-values were <0.05.

Results

Effects on blood pressure

Left renal artery clipping led to an increase in systolic blood pressure from 126 ± 3 mmHg to 193 ± 3 mmHg (P < 0.05). Left renal denervation attenuated the increase in blood pressure to 179 ± 12 mmHg (NS vs clipping). Treatment with amlodipine and mibe- fradil decreased blood pressure to 127 ± 14 and 130 ± 11 mmHg, respectively (P < 0.05 vs clipping + denervation).