by Southern blotting and hybridization with D_3- and β‐actin specific probes derived from rat brain RNA. The renal effects of 7-OH-DPAT were not influenced by the selective D_3 receptor antagonist S(−)-sulpiride but abolished by pre-treatment with the D_3 antagonist 5,6-dimethoxy-2-(di-n-propylamino)indane (U-99194A). Taken these results together, 7-OH-DPAT appears to affect glomerular and tubular function by specific D_3 receptor activation.

In a second set of experiments renal blood flow (RBF) was measured by an electromagnetic flow transducer placed on the left renal artery. Also in this setting, 7-OH-DPAT (1.0 μg/kg/min) increased GFR by 19±3%. Interestingly, RBF was significantly reduced by 26±3% compared with baseline. Renal vascular resistance was significantly elevated by 25±4% due to 7-OH-DPAT infusion. Haemodynamic changes of the kidney were not influenced by pre-treatment with S(−)-sulpiride but were completely abolished by pre-treatment with U-99194A. The hypothesis that 7-OH-DPAT infusion might cause vasoconstriction of postglomerular vessels was tested employing micropuncture experiments. Stop flow pressure (SFP) was measured in the early proximal tubule as an indicator of the glomerular capillary pressure. Compared with infusion of isotonic saline, 7-OH-DPAT (1.0 μg/kg/min) significantly increased SFP while MAP was not altered. Furthermore, hydrostatic pressure in the efferent arteriole was reduced during 7-OH-DPAT infusion. Taken together, the results of the micropuncture experiments support the hypothesis of a 7-OH-DPAT-induced postglomerular vasoconstriction.

The role of D_3 receptors in the regulation of kidney function under pathophysiological conditions is unclear. Asico et al. [4] described that transgenic mice lacking both D1 receptors developed systemic hypertension and had an impaired ability to excrete an acute saline load. In addition, renal renin activity was higher in the homozygous than in wild-type mice. Due to its expression in juxtaglomerular cells the D_3 receptor may negatively affect renin secretion [5]. From these data it was suggested that D_3 receptors—possibly by impairment of the renal excretory capacity for sodium or increased renin excretion—may play a pathogenetic role in some forms of hypertension. However, 7-OH-DPAT induced a similar diuresis and natriuresis in spontaneously hypertensive and Wistar–Kyoto rats [6].

In summary, pharmacological activation of dopamine D_3 receptors affects tubular function and renal haemodynamics in anaesthetized rats, the latter possibly by post-glomerular vasoconstriction. Whether D_3 receptors are involved in the pathophysiology of systemic or renal haemodynamics remains to be determined.

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References


Treatment with the angiotensin II antagonist valsartan in patients with chronic renal failure and hypertension

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Introduction

Angiotensin II (Ang II) type I receptor antagonists are a class of drugs derived from imidazole-5-acetic acid. Losartan is the most widely studied receptor antagonist up to now and comparable with angiotensin-converting enzyme inhibitors (ACEIs) in its blood pressure lowering effect in patients with essential hypertension [1,2]. Direct blocking of the Ang II type 1 receptor-binding site by Ang II antagonists may provide the advantage of a more specific blocking of Ang II action by additionally inhibiting the Ang II generation caused...
by tissue enzymes (e.g. chymases or CAGE) [3]. While there are an increasing number of reports about the potency of Ang II receptor antagonists to lower blood pressure in essential hypertension [4] and benefits in cardiovascular disease [5], there is not much information about their antihypertensive and antiproteinuric (‘nephroprotective’) effects in patients with arterial hypertension and impaired renal function.

**Patients and methods**

The effects of the Ang II antagonist valsartan (80 mg/day) on proteinuria and glomerular permselectivity were studied in patients with chronic renal failure during a 6-month treatment period. We followed a double-blind, randomized, placebo-controlled study [treatment group (V-group); n = 5, age: 57 ± 7 years, serum creatinine: 365 ± 122 μmol/l; placebo group (P-group): n = 4, age: 62 ± 11 years, serum creatinine 346 ± 61 μmol/l]. Study parameters included blood pressure, 24 h proteinuria, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) as determined by inulin and PAH clearance. Changes in glomerular permselectivity were assessed by measuring the fractional clearances of neutral dextrans by HPLC gel permeation chromatography.

**Fig. 1.** (A) Proteinuria and (B) albuminuria during 6 months of treatment with valsartan 80 mg/day (V-group, n = 5) or placebo (P-group, n = 4) in patients with renal failure. The relative changes vs the run-in phase (averaged, set to 100%) are shown and, additionally, the absolute daily excretion (mg/24 h) during run-in and after 6 months of treatment is indicated. Values are given as mean ± SEM. Changes vs the run-in phase are indicated by asterisks, *P < 0.05. Differences between both study groups during the treatment phase are tested by MANOVA and indicated by | | .

**Fig. 2.** Change of the glomerular sieving coefficients for neutral dextrans of different Einstein stokes radii (fractional dextran clearances) after 6 months of treatment with (A) valsartan 80 mg/day (V-group, n = 5) or (B) placebo (P-group, n = 4) in patients with renal failure. Reference values of healthy controls (n = 10) are shown. Data are given as mean ± SEM. Differences between baseline values in the study groups and the sieving coefficients of healthy controls are tested by i-test for independent samples, *P < 0.05, **P < 0.01.
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**Results**

Valsartan lowered the mean arterial pressure on average by 13±7 mmHg during 6 months treatment \((P<0.05)\). Average blood pressure reduction over 6 months was significantly different between the V-group and the P-group.

Baseline serum potassium concentrations in the V-group moderately increased from 4.4±0.4 mmol/l to 4.9±0.5 mmol/l after 3 months of valsartan treatment \((P<0.05)\) and remained almost unchanged thereafter.

In the V-group, baseline GFR was 20±7 ml/min in the run-in period and averaged 18±6 ml/min for the three measurements during the treatment phase (NS). In the P-group, GFR changed from 19±5 ml/min to 21±8 ml/min (NS). RBF decreased slightly over time from 152±47 to 140±47 ml/min in the V-group and from 143±53 to 129±55 ml/min in the P-group. The trend between the groups concerning ERPF and RBF was not significantly different with regard to the whole observation period.

After 6 months of valsartan treatment, proteinuria was reduced by 396±323 mg/24 h (26±18%) and albuminuria by 531±499 mg/24 h (41±21%) with respect to baseline values \((P<0.05)\). In the P-group, both proteinuria and albuminuria increased slightly with time (by 30±43% and 30±54%, respectively, NS) (Figure 1).

The fractional clearances of high molecular weight dextrans >66 Å were significantly reduced after 6 months of valsartan treatment \((P<0.05)\), indicating a reduction of the glomerular shunt volume by 54±20% \((P<0.05)\) according to the model of Deen et al. [6]. The mean pore size radius of the glomerular membrane remained unchanged. This effect was independent of glomerular haemodynamic changes (Figure 2).

**Conclusions**

Our findings with the Ang II antagonist valsartan show a sustained reduction in blood pressure and proteinuria even in patients with advanced renal failure. While GFR and ERPF remained nearly stable, this effect could be attributed to an improvement in glomerular permselectivity. A preserved excretory renal function together with functional benefits in glomerular permselectivity may recommend this class of antihypertensives as a 'nephroprotective alternative' to ACEIs. This will require further long-term studies.

**References**


**A randomized, double-blind, parallel study on the safety and antihypertensive efficacy of losartan compared to captopril in patients with mild to moderate hypertension and impaired renal function**

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The angiotensin II (Ang II) pathway plays an important role in the progression of renal disease. The renal effects of Ang II are also crucially involved in maintaining blood pressure (BP) in hypertension.

This international multicentre study was conducted to compare the effects on blood pressure, creatinine clearance, proteinuria and lipids of the Ang II AT1 receptor antagonists losartan (LOS) and captopril (CAP) in patients with mild to moderate hypertension and impaired renal function. Another aim of the present study was to evaluate the safety and tolerability of LOS in this special group of patients which are not yet well documented.

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