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ORIGINAL ARTICLE

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# Is enalapril adequate for the prevention of renal tissue damage caused by unilateral ureteral obstruction and/or hyperoxaluria?

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**Abstract** Unilateral ureteral obstruction (UUO) and hyperoxaluria (HOX) can lead to end-stage renal disease with tubulointerstitial fibrosis. We investigated the effects of enalapril (E), an ACE-inhibitor, on rat kidneys with either UUO or HOX. Sham-operated, UUO, HOX, UUO + HOX, UUO + E and HOX + E rats were killed 14 days after UUO and/or HOX was initiated. Rat kidney sections were histologically scored for tissue damage and monocyte/macrophage infiltration was demonstrated with ED1 antibody and measured by computer image analysis software. Serious glomerular and tubulointerstitial damage was found for UUO and HOX, consisting of glomerular basement membrane thickening, tubular dilatation/collapse, tubular basement membrane thickening and the infiltration of mononuclear leucocytes (mainly macrophages). For HOX, calcium oxalate crystals were visible. Neither the scored histological parameters nor monocyte/macrophage infiltration was significantly decreased when E-treated were compared with untreated groups. We conclude that E did not ameliorate the parameters scored in either UUO or HOX. This being contrary to findings by other research groups, we hypothesize that E may be effective only in short-term UUO/HOX, with transforming growth factor, TGF-$\beta$1, formation becoming partly independent of Ang II in late-stage UUO/HOX, or other fibrogenic cytokines than TGF-$\beta$1 becoming predominant.

**Keywords** Ureteral obstruction · Enalapril · Hyperoxaluria · Renal damage · ED1

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## Introduction

Unilateral ureteral obstruction (UUO) initiates renal injury [13] characterized by tubular dilatation and/or atrophy, infiltration of leucocytes (macrophages), fibroblastic proliferation and an increase in matrix proteins, resulting in progressive interstitial fibrosis [8, 10] and ultimately even end-stage renal disease [13].

Hyperoxaluria (HOX) causes nephrolithiasis [17] and tubulointerstitial (TI) damage [28, 30]. Calcium oxalate (CaOx) crystals are retained within the tubules. Small crystals are endocytosed [16, 31], large ones overgrown by tubular epithelium and incorporated interstitially inducing inflammation [16, 19, 27, 28]. Crystals are surrounded by infiltrates (mainly macrophages and giant cells), glomerular damage, tubular dilatation, epithelial damage, Tamm-Horsfall protein deposition and TI fibrosis [11, 20]. Chronic HOX may also progress to chronic renal failure [28].

The renin-angiotensin (Ang II) system is upregulated in UUO and involved in TI fibrosis in both diseases [12, 14, 28]. Ang II stimulates transforming growth factor-$\beta$1 synthesis (TGF-$\beta$1) [10] in damaged tubular epithelial cells and macrophages [9, 15, 24, 28]. TGF-$\beta$1 modulates fibroblast-myofibroblast transformation, stimulates extracellular matrix (ECM) production, inhibits ECM degradation, participates in apoptosis and is chemoattractive for monocytes/macrophages [1, 10, 15, 23, 24].

Angiotensin-converting enzyme (ACE) inhibitors or Ang-II receptor antagonists might thus ameliorate the effects of UUO or HOX. We investigated whether the ACE inhibitor enalapril (E) reduces renal damage and

infiltration of monocytes/macrophages using an UUO/HOX rat model.

## Materials and methods

### Animals and experimental protocol

This study was approved by the Institutional Ethics Committee for Animal Experiments (no: 102.00.05) and is in accordance with the NIH Guide for Care and Use of Laboratory Animals. After 4 days of acclimatization, male Wistar rats (200–300 g; Harlan, Germany) were divided into six groups: sham-operated ($n=6$), UUO ($n=6$), HOX ($n=7$), UUO + HOX ($n=5$), UUO + E ($n=7$) and HOX + E ($n=7$). The three HOX groups started with 0.8% ethylene glycol (oxalate-precursor) in their drinking water. At day 6, the right proximal ureter was ligated (5-zero silk suture) in the three obstruction groups, UUO, UUO + HOX and UUO + E. In the other three groups, the right ureter was only manipulated. During the operation, bladder urine was taken from the three HOX groups, HOX, UUO + HOX and HOX + E, and the presence of CaOx crystals was confirmed. The groups UUO + E and HOX + E received enalapril maleate (MSD, St.Germain Laprade, France, SP2111) in their drinking water (200 mg/l), from the day after operation until the end of the study.

### Tissue preparation

All animals were killed 2 weeks postoperatively. At the time of death, crystalluria was examined in the urine from the renal pelvis and/or bladder. Complete ureteral obstruction was shown to be present by the absence of antegrade methylene blue drainage from the pelvis to the bladder. After being perfused with Dulbecco's phosphate buffered saline solution through the infrarenal aorta until clear of blood-borne cells, the kidneys were harvested, weighed, halved and snap-frozen in isopentane/liquid nitrogen or preserved in paraformaldehyde/PBS. Fixed kidney-parts were embedded in paraffin and sectioned (showing cortex, medulla and papilla) for histology and immunohistochemistry.

### Histological damage

Sections were periodic acid-Schiff (PAS) stained. Histological damage was evaluated semi-quantitatively on a scale of 0 to 3 (0 = no damage; 0.5 = weak; 1 = moderate; 2 = severe; 3 = very severe). Tubular dilatation, tubular basement membrane (TBM) thickening, tubular collapse and crystal deposition (polarized light) were scored separately for the proximal tubule, distal tubule and collecting duct. Infiltration of mononuclear cells (MNC) was evaluated for the cortex and medulla. Finally, we counted the fraction of glomeruli with glomerular basement membrane (GBM) thickening in three random places. Two observers carried out all examinations blinded to the treatment group. Random slides were shown to a kidney pathologist who confirmed their results.

### Immunohistochemistry for ED1

Monocytes and macrophages were identified using ED1 (a specific immunohistochemical marker) mouse anti-rat monoclonal antibody [2, 30, 31].

Deparaffinized sections (5 $\mu$m) were boiled for 15 min with 10 mmol/l citrate buffer (pH 6.0), preincubated with 10% normal goat serum, washed and incubated with a mouse monoclonal ED1-antibody (Serotec, Oxford, UK; 1/1000) or PBS (negative control). Primary antibody was detected by biotinylated anti-IgG and streptavidin-labeled peroxidase (Biogenex, San Ramon, Calif, USA). All sections were counterstained with Mayer's hematoxylin.

### ED1 staining analysis

We used KS400 v2.0 image analysis software (Kontron Electronics, Munich, Germany). A 3CCD Sony color videocamera (DXC-930) was mounted on a Zeiss Axioplan microscope (Zeiss, Oberkochen, Germany) with a 40× objective and connected to a FG1 frame grabber (Kontron). Fifteen random areas (five cortex, five outer medulla, five inner medulla) of 512×512 pixels were recorded. The ED-1positive area was expressed as a fraction of the total area (excluding tubular lumina).

### Statistical analysis

Group data were compared using the (exact) Mann-Whitney U-test on SPSS PC software. A $P$-value of $<0.05$ was considered significant.

## Results

### Histological damage

#### *Unilateral ureteral obstruction*

The results are given in Table 1. The obstructed kidneys from the UUO group showed serious tissue damage (Fig. 1A): hydronephrosis, GBM-thickening, dilatation of distal tubules and collecting ducts, TBM-thickening, tubular collapse (mainly proximal and distal tubules) and infiltration of MNC compared to the sham-group and contralateral kidneys. The interstitial tissue was widened by matrix deposition and cellular infiltration and/or proliferation. ED1-staining demonstrated a large proportion of macrophages. The unobstructed left kidneys showed no signs of glomerular or tubulointerstitial damage.

In the UUO + E group, E did not prevent the histological damage produced by UUO (Fig. 1B). The only significant difference between the UUO group and the UUO + E group was an increased collapse of distal tubules in the untreated obstruction group.

#### *Hyperoxaluria*

CaOx-crystals were present all along the nephron, predominating in the outer medullar proximal tubules. All scored parameters and MNC-infiltration were significantly raised compared to the sham group. As HOX causes damage in both kidneys, left and right kidneys of the HOX group were equally effected. The same was true for the treatment group, HOX + E. The hyperoxaluric groups with (HOX + E) and without (HOX) E-treatment showed no differences for any of the histological damage parameters (Fig. 2).

**Table 1** Results of histological damage (PAS-staining); p = proximal tubule; d = distal tubule; c = collecting duct; cx = cortex; m = medulla; GBM-thickening = thickened glomeruli/total number of glomeruli. Other parameters: 0 = no damage; 0.5 = weak damage; 1 = moderate damage; 2 = severe damage; 3 = very severe damage

| Group | GBM thickening | | Tubule | Tubular dilatation | | TBM thickening | | Tubular collapse | | Crystal deposition | | Site | MNC infiltration | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Right | Left | | Right | Left | Right | Left | Right | Left | Right | Left | | Right | Left |
| Sham | 0.074 | 0.083 | P | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 | 0.0 | 0.0 | CX | 0.1 | 0.3 |
| | | | D | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | M | 0.1 | 0.0 |
| | | | C | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | | | |
| UUO | 0.488 | 0.042 | P | 0.3 | 0.2 | 1.3 | 0.0 | 1.6 | 0.0 | 0.0 | 0.0 | CX | 2.0 | 0.1 |
| | | | D | 1.3 | 0.0 | 1.5 | 0.0 | 1.5 | 0.0 | 0.0 | 0.0 | M | 1.6 | 0.1 |
| | | | C | 1.0 | 0.1 | 0.7 | 0.0 | 0.8 | 0.0 | 0.0 | 0.0 | | | |
| HOX | 0.255 | 0.285 | P | 1.0 | 1.1 | 0.9 | 0.5 | 1.2 | 0.8 | 1.6 | 1.6 | CX | 2.1 | 1.7 |
| | | | D | 1.6 | 1.7 | 1.1 | 1.1 | 0.8 | 0.7 | 0.8 | 0.9 | M | 1.2 | 0.9 |
| | | | C | 1.4 | 0.9 | 0.6 | 0.4 | 0.0 | 0.0 | 0.8 | 0.8 | | | |
| UUO + HOX | 0.554 | 0.200 | P | 0.4 | 0.9 | 0.9 | 0.6 | 2.0 | 0.9 | 0.5 | 0.9 | CX | 2.2 | 1.1 |
| | | | D | 2.3 | 1.5 | 1.1 | 0.8 | 0.8 | 0.6 | 0.2 | 0.7 | M | 2.0 | 0.7 |
| | | | C | 2.5 | 1.1 | 0.7 | 0.4 | 0.0 | 0.0 | 0.3 | 0.6 | | | |
| UUO + E | 0.481 | 0.061 | P | 0.4 | 0.1 | 0.9 | 0.0 | 2.2 | 0.0 | 0.0 | 0.0 | CX | 2.0 | 0.1 |
| | | | D | 2.1 | 0.1 | 1.5 | 0.1 | 0.3 | 0.1 | 0.0 | 0.0 | M | 1.6 | 0.0 |
| | | | C | 2.2 | 0.2 | 1.2 | 0.0 | 0.1 | 0.0 | 0.0 | 0.0 | | | |
| HOX + E | 0.340 | 0.405 | P | 1.3 | 1.4 | 0.6 | 0.6 | 1.1 | 0.7 | 2.1 | 2.1 | CX | 1.9 | 1.6 |
| | | | D | 1.4 | 1.6 | 1.2 | 1.3 | 0.5 | 0.7 | 1.1 | 1.1 | M | 1.1 | 0.9 |
| | | | C | 0.9 | 0.7 | 0.7 | 0.4 | 0.2 | 0.1 | 0.8 | 0.6 | | | |

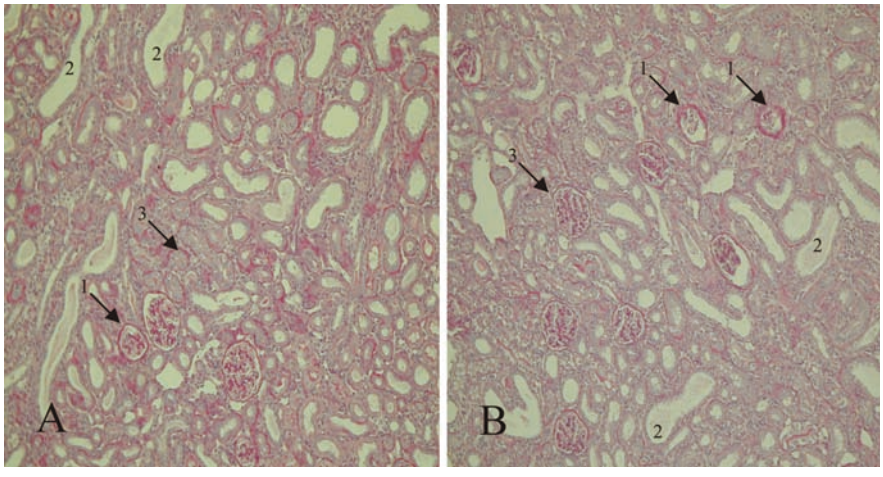


**Fig. 1** Micrographs showing details of histological damage in the renal cortex of a rat **A** with UUO and **B** with UUO + E at 100× magnification. PAS-staining was used. *1* = GBM-thickening; *2* = tubular dilatation; *3* = tubular collapse

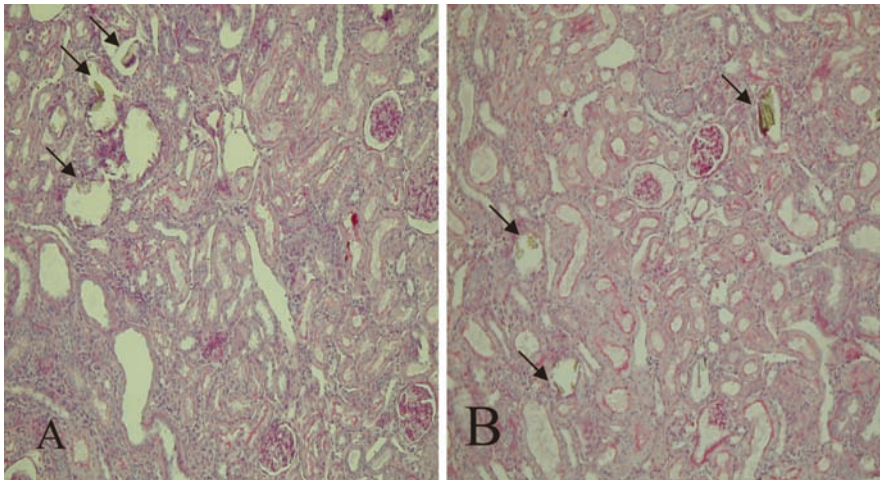


**Fig. 2** Micrographs showing details of histological damage in the renal cortex of a rat **A** with HOX and **B** with HOX + E at 100× magnification. PAS-staining was used. *Arrows* indicate crystals

*Unilateral ureteral obstruction and hyperoxaluria*

Compared to the sham group, the group receiving the combination of challenges, UUO + HOX showed the most serious damage to the obstructed right kidneys comprising: GBM-thickening, tubular dilatation, TBM-thickening, tubular collapse, crystal deposition and infiltration of MNC. Compared to UUO alone, dilatation of the distal tubules and collecting ducts and proximal crystal deposition were higher in the presence of HOX (UUO + HOX group). Compared to HOX alone (HOX group), GBM-thickening, dilatation of the distal tubules and collecting ducts and MNC infiltration of the medulla were higher for the right kidneys of the combined challenge group (UUO + HOX), while crystal deposition along the entire nephron was significantly lower for the combined group. The left kidneys of both groups were similar.

## Immunohistochemistry for ED1

ED1-positive cells (monocyte/macrophage) were significantly increased in the cortex, outer medulla and inner medulla of the right kidneys of the groups UUO, HOX, UUO + HOX, UUO + E and HOX + E as compared to the sham group ($P < 0.01$). Compared to their contralateral kidneys, they were also increased in the UUO and UUO + E groups ($P < 0.05$). In the three HOX groups the presence of ED-1 positive cells was comparable for both kidneys (Table 2).

The contralateral left kidneys in the sham and UUO groups were comparable. Those in the three HOX groups HOX, UUO + HOX, and HOX + EG5 and in the UUO + E group had more ED1-positive cells than the SHAM and UUO groups ($P < 0.01$). The left kidneys of the combined challenge group UUO + HOX had fewer macrophages ($P < 0.05$) than the two groups receiving HOX as a single challenge, HOX and HOX + E, suggesting a 'protective effect' of contralateral UUO.

As for the effect of E, no significant decrease in macrophages was found between the right kidneys of the UUO groups with or without E (UUO and UUO + E) (Fig. 3), nor between those of the HOX challenged groups with or without E (HOX and HOX + E). In fact, the outer medulla of the HOX + E group contained more ED1-positive cell infiltration than that in the HOX group ($P < 0.01$). The same was true for the contralateral left kidneys, where the E-treated HOX group (HOX + E) showed more ED1 infiltration than the HOX group for all of the three places scored ($P < 0.01$).

We observed a spectrum of histological changes following UUO, many of which have been documented previously [3, 8, 10]. Although in some studies glomeruli appeared rather normal after UUO [10, 29], we found GBM-thickening in 50% of cases, maybe as part of the onset to glomerular sclerosis. This confirms data showing thickening of the GBM after various UUO durations [3]. The interstitial tissue was expanded in UUO, mainly by infiltrating monocytes/macrophages, but also by fibroblast proliferation and matrix protein deposition [10, 26].

**Table 2** Results of immunohistochemistry for ED1 expressed in ED1-postive area/total tissue area

| | Cortex | | Outer medulla | | Inner medulla | |
|---|---|---|---|---|---|---|
| | Right | Left | Right | Left | Right | Left |
| Sham | 0.0010 | 0.0021 | 0.0008 | 0.0005 | 0.0009 | 0.0009 |
| UUO | 0.0228 | 0.0019 | 0.0234 | 0.0015 | 0.0278 | 0.0008 |
| HOX | 0.0194 | 0.0205 | 0.0156 | 0.0152 | 0.0291 | 0.0342 |
| UUO + HOX | 0.0197 | 0.0133 | 0.0146 | 0.0088 | 0.0254 | 0.0183 |
| UUO + E | 0.0269 | 0.0043 | 0.0318 | 0.0036 | 0.0278 | 0.0064 |
| HOX + E | 0.0183 | 0.0238 | 0.0130 | 0.0216 | 0.0324 | 0.0360 |

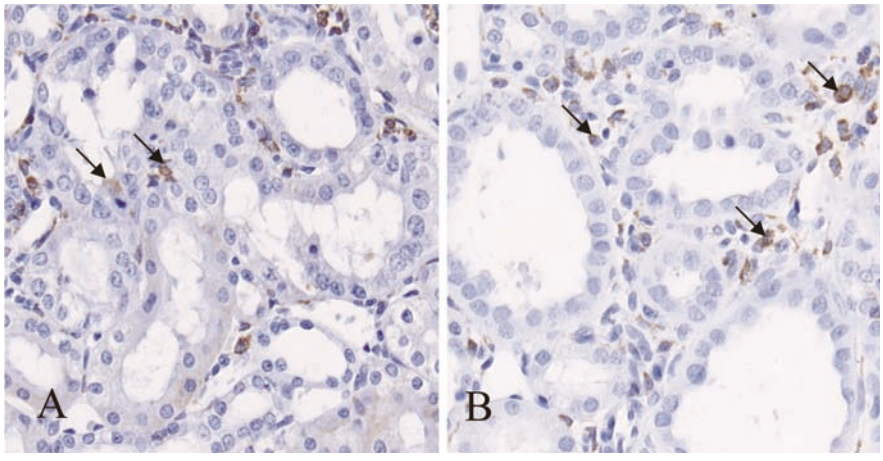


**Fig. 3** Micrograph of a rat kidney (cortex) **A** with UUO and **B** with UUO + E, stained for ED1 at 400× magnification. The *brown colored cells* (*arrows*) are ED1-positive monocytes/macrophages

Renal CaOx deposition has been associated with kidney stone disease [17, 28, 30]. Rats with EG induced HOX display many histological changes also observed in UUO. Glomerular damage consisted of GBM-thickening (25% of cases), frequently coupled with adhesion between the parietal and visceral layer of Bowman's capsule. Similar phenomena have already been documented [30]. CaOx crystals were primarily seen in the lumina of proximal tubules, but also inside distal tubules, collecting ducts and occasionally interstitially.

Macrophages are found interstitially in all kidneys with progressive renal disease. Circulating monocytes migrate into inflamed renal interstitial tissue under the direction of chemotactic stimuli and adhesion molecules [4], also produced by the macrophages [6]. The density of infiltrating mononuclear cells correlates well with declining renal function [22]. We used the ED1-marker [2] to demonstrate monocytes/macrophages. In control rats, ED1-positive macrophages are seen in the perivascular interstitial tissue and around glomeruli [31]. In UUO and HOX they are found throughout the interstitial tissue both in the cortex and medulla [3, 31], preferably surrounding the distal tubular epithelium [25]. We found increased ED1-positive staining in both the UUO and HOX groups.

E has been shown to blunt the increase of interstitial volume, collagen type-IV deposition (21%) and ED1-positive cells (89%) in UUO after 3–5 days [10] and after 3–10 days with delayed E treatment [7]. In contrast, we did not find any ameliorating effect for E. Since TGF-$\beta$1 concentration should be reduced by inhibition of Ang II formation, we expected a decrease in infiltration of ED1-positive cells and reduced histological damage.

What could explain this observation? The rats received 200 mg/l E, a dose frequently used in other investigations [6, 7, 8, 10]. All animals emptied their water containers as indicated by the presence of crystals in the rats whose containers also contained ethylene glycol. Previously, a low dose (50 mg/l) of ACE-inhibitor was shown to better preserve structure in a nephrectomy model than a high dose (200 mg/l). The low dose blocked endothelial ACE and the high dose blocked endogenous renal ACE [5].

Artifacts due to tissue-preparation or staining are excluded as significant differences are clearly present between the sham, UUO, HOX and UUO/HOX groups, both histologically and for ED1 staining. Finally, all research was performed with the observer blind to the treatment group, ruling out observer-bias.

Is E only effective in short-term UUO? Our work with UUO and/or HOX had a duration of 14 days versus a maximum of 10 days in Ishidoya et al.'s study [7]. It is possible that TGF-$\beta$1 is formed partly independent from Ang II in late-stage UUO, or that other fibrogenic cytokines take over and E-effects are by-passed. Platelet-derived growth factor [21], fibroblast growth factor, interleukin-1, TNF-$\alpha$ and TGF-$\alpha$ [18] may also contribute to renal fibrosis. Little is known about the effect of E on their expression. Ang II stimulates TGF-$\beta$1 production in renal tubular cells and macrophages [9, 15, 24, 28] but is not always essential for upregulated renal expression of TGF-$\beta$1 in renal injury [4].

## Conclusions

We found serious glomerular and tubulointerstitial damage after 2 weeks of UUO and/or HOX compared to the sham-operated group, with macrophage infiltration present in the cortex, outer and inner medulla. E did not seem to have any ameliorating effect for parameters scored in either UUO or HOX. Further detailed studies are needed before enalapril can be used clinically.

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