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Tubuloglomerular Feedback Response in the Contralateral Kidney after 24-hour Unilateral Ureteral Obstruction

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ABSTRACT

Reduction of the functioning renal mass by unilateral nephrectomy or unilateral ureteral occlusion (UUO) leads to increased function of the remaining nephrons, an important factor being the glomerular filtration rate (GFR). GFR can be modified via the tubuloglomerular feedback control (TGF), which senses the distal delivery of fluid and alters the tonus of the glomerular arterioles. The aim of the present study was to investigate the TGF sensitivity in the intact left kidney of rats after 24 hours of right ureteral occlusion. Using a micropuncture technique, proximal tubular stop-flow pressure (P_{sf}), as a relative index of glomerular capillary pressure, was measured upstream to the block, while late proximal segments were perfused with Ringer solution (rates 0-40 nl/min). The maximal drop in P_{sf} and the tubular flow rate at which 50 % of this response was achieved, the turning point (TP), were determined. Considerable decrease in the sensitivity of the TGF system in the contralateral kidney during UUO was indicated by a significantly higher TP as compared with control rats (sham operation), viz. 29 v. 19 nl/min. Maximal P_{sf} drop after UUO was significantly less than in the controls (6 v. 12 mm Hg). Reduced TGF sensitivity in the contralateral kidney after protracted UUO is a prerequisite for that kidney's increased excretion of salt and water to compensate for the loss of functioning renal mass.

INTRODUCTION

The effects of unilateral ureteral obstruction (UUO) have been extensively investigated with regard to renal function and haemodynamics (19,20), with methods including micropuncture experiments (4). Following 24 hours of UUO the sensitivity of the tubuloglomerular feedback control (TGF) mechanism in the obstructed kidney was found to be considerably enhanced (18).

Less interest has been focused on the contralateral, intact kidney.

Haemodynamic studies (9,16,17) have shown only small changes in renal blood flow. In experiments with micropuncture technique (3) the function of the contralateral kidney was found to be essentially unaltered after 24 hours of UUO.

The loss of functioning nephrons as a result of unilateral nephrectomy or UUO is compensated by increase in the function of the remaining kidney, a phenomenon that now is well documented. The glomerular filtration rate (GFR) is one important factor determining the rate of fluid excretion, and GFR can be modified through the action of the TGF system. The mechanism underlying this adaptive compensation is not fully understood, and the present experiments were designed for investigation of the TGF mechanism in the intact kidney during 24 hours of contralateral UUO. These studies were made on rats, with measurement of the proximal tubular stop-flow pressure. The TGF sensitivity was found to be reset to a low level in the contralateral kidney after 24 hours of UUO, allowing an increase in GFR and in delivery of fluid to the distal nephron. These observations can explain the increase in renal function that takes place in the studied situation.

METHODS

The experiments were conducted on male Sprague-Dawley rats weighing 200-250 g. Ligation of the right ureter or sham operation were performed in Brietal anaesthesia (Lilly, USA), 50 mg/kg body weight (BW) intraperitoneally (ip). After the operation the rats were allowed free access to water. Twenty-four hours later they were anaesthetized with Inactin^{R} (Byk, Constanz, FRG), 120 mg/kg BW ip and placed on a servo-regulating heating pad. A free airway was ensured by tracheostomy. The femoral artery and vein were cannulated for recording of arterial pressure and intravenous infusion of saline solution, respectively, the latter at a rate of 0.5 ml/h·100 g·BW. The left, unobstructed kidney was dissected free, placed in a lucite cup and covered with mineral oil to prevent drying. The ureter was cannulated to ensure free urine flow.

To characterize the TGF system, the proximal tubular stop-flow pressure technique was used during perfusion of the distal nephron with a Ringer solution according to a previously described method (13). To outline the nephron and measure the free-flow proximal pressure (P_t), a 3 μm thin glass pipette was inserted into a proximal tubular segment. This pressure pipette was connected to a servo-nulling device (WP Instr, New Haven, Conn, USA). To achieve a situation of stop-flow pressure (P_{sf}), a solid paraffin wax block was injected, distal to the puncture site of the pressure pipette, into the early proximal tubule (6). A third micropipette, connected to a calibrated microperfusion pump (Hampel, Frankfurt, FRG), was used to perfuse the loop of Henle of the same nephron at

flow rates ranging from 0-40 nl/min, with stepwise increments of 5 nl/min. The Ringer perfusion solution comprised 140 nM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 4 mM $NaHCO_3$, 7 mM urea and 2 g/l lissamine green, pH 7.4. P_{sf} was recorded continuously on a Servogor^R recorder during loop perfusion at different rates. The nephron was perfused for 2-3 minutes at each perfusion rate in order to obtain stable pressure measurements. TGF was determined in three nephrons in each animal.

The maximal decrease in P_{sf} (ΔP_{sf}) was measured during perfusion at 40 nl/min, and the turning point (TP) of the feedback response was defined as the perfusion rate at which 50 % of ΔP_{sf} was obtained. To calculate the mean response curve, information from all nephrons was used by applying a perviously described normalization method (14). The normalized data were then pooled and fitted to the equation describing P_{sf}, using a curve-fitting programme (Minuit. Cern.), which utilizes a nonlinear least square procedure:

$$P_{sf} = P_{sfmin} + \Delta P_{sf} / 1 + e^{w(PR-TP)}$$

where P_{sf} is the stop-flow pressure, P_{sfmin} is the minimal stop-flow pressure and ΔP_{sf} is the maximal stop-flow pressure response occurring on increase of the distal delivery of fluid, TP is the turning point, PR the end-proximal perfusion rate and w the factor determining the width of the perfusion rate interval during which the decrease in stop-flow pressure occurs.

For tests of significance the grouped Student`s t-test was used, and values given in the following are means + SE. A p value of < 0.05 was regarded as significant.

RESULTS

The results are summarized in Table 1 and Fig. 1. The mean arterial blood pressure (P_a) did not differ significantly between the rats subjected to UUO and the control rats with sham operation. The TGF determinations showed that the sensitivity was much lower in the contralateral kidney after 24 hours of UUO than in the controls, indicated by a TP of 29 nl/min and ΔP_{sf} 6 mm Hg in the former group as compared with 19 nl/min and 12 mm Hg in the latter. The intratubular pressure (P_t) was significantly higher in the contralateral kidney after 24 hours of UUO than in the control rats (13 v. 11 mm Hg), while the P_{sf} values did not significantly differ. The computed mean response curves in Fig.1 illustrate the reduced TGF sensitivity in the contralateral kidney after 24 hours of UUO compared with the sensitivity in the control rats with sham operation.

Table 1. Effects of unilateral ureteral obstruction (UUO) on the tubuloglomerular feedback in the contralateral kidney

		Controls (sham operation)	Contralateral kidney after UUO for 24 hrs	
P_a	(mm Hg)	117 + 7	108 + 4	NS
P_t	(mm Hg)	11.1 + 0.9	13.4 + 0.4	$p < 0.01$
P_{sf}	(mm Hg)	32.1 + 1.7	34.1 + 0.8	NS
ΔP_{sf}	(mm Hg)	12.0 + 0.9	5.9 + 0.7	$p < 0.001$
TP	(nl/min)	19.2 + 1.1	29.3 + 1.5	$p < 0.001$
No of investigated nephrons		9	18	

P_a = arterial blood pressure, P_t = intratubular pressure, P_{sf} = maximal stop-flow pressure, ΔP_{sf} = maximal drop in stop-flow pressure, TP = turning point.

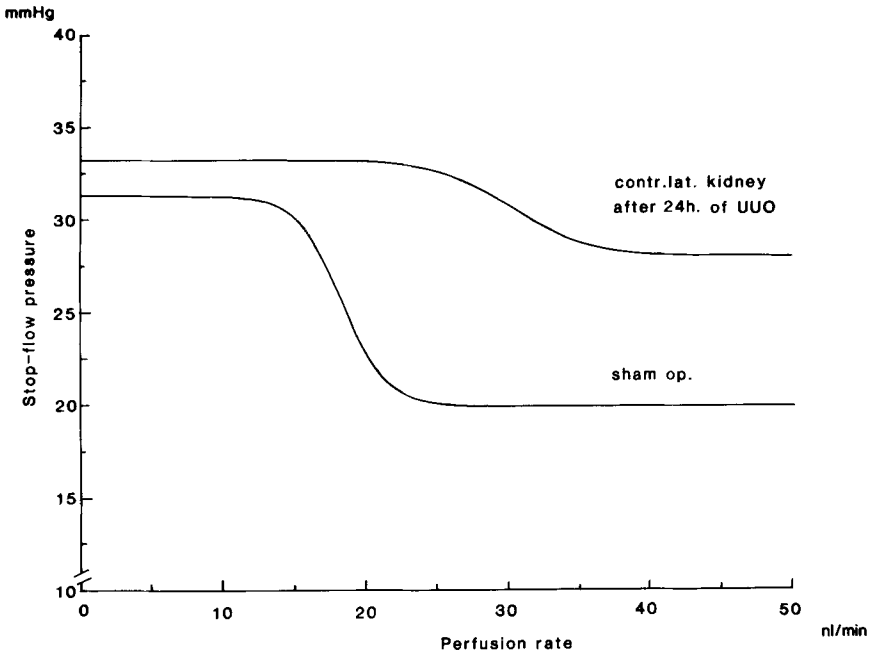

Fig. 1. Computed mean response curve for the contralateral kidneys during unilateral ureteral obstruction compared with curve for the controls with sham operation.

DISCUSSION

GFR is one factor that influences the excretion rate of salt and water. In the regulation of GFR the tubuloglomerular feedback control is an important mechanism (21), which can influence the rate of fluid delivery to the distal nephron by adjusting the tonus of the glomerular arterioles. The sensitivity of this mechanism can be reset by changes in the extracellular fluid volume and arterial blood pressure, mediated by changes in interstitial hydrostatic and oncotic pressures (12).

There are reasons for believing that the following sequence of events may occur within the obstructed kidney during UUO: After the obstruction, a rise in pelvic pressure increases the renal interstitial hydrostatic pressure and reduces the interstitial oncotic pressure (11). These changes, resembling those found during volume expansion, will reduce TGF sensitivity and ultimately abolish the TGF response during the first few hours of obstruction. During this phase there is strong vasodilation (17), with increased renal blood flow and a rise in glomerular capillary pressure (15) induced by the production of prostaglandins (1,5,10,15). Later during UUO there is increasing vasoconstriction (4, 17) and the TGF response returns. After 24 hours of UUO the TGF sensitivity is very high, with a low turning point.

In earlier studies on the remaining kidney shortly after uninephrectomy, the TGF sensitivity was found to be reset to a low level 30 minutes after removal of the kidney, influenced by prostaglandin production (8). Further, the interstitial pressure in the remaining kidney was changed shortly after nephrectomy (7), with rise in interstitial hydrostatic, and fall in oncotic pressure. Unilateral nephrectomy also resulted in dilation of the vasculature in the remaining kidney (8). In other experiments (present authors, unpublished observations) it was found that UUO leads within 2 - 3 hours to reduction of TGF sensitivity in the contralateral kidney. As was found in the present study, this low sensitivity persists even after 24 hours of UUO. Concomitant changes in renal interstitial pressure may be the cause of this sensitivity reduction, but no measurements have yet been made to prove the possibility.

In summary, one prerequisite for the increased excretion rate of salt and water via the contralateral kidney during 24 hours of UUO is a reduction of the TGF sensitivity, as documented in this study. This event may possibly be caused by changes in prostaglandin production. The involvement of prostaglandin production may then be similar to that occurring after unilateral nephrectomy.

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