Renal endothelin system in obstructive jaundice: its role in impaired renal function of bile-duct ligated rats

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1. Obstructive jaundice predisposes the kidney to acute renal failure. Endothelin (ET), a potent renal vasoconstrictor and modulator of the tubular action of arginine vasopressin, has been suggested to play a pathogenetic role in acute renal failure. In the present study we therefore investigated renal function and the renal ET system in rats on day 4 after bile-duct ligation (BDL) or sham-operation (SO), without (n = 7 in each group) and with treatment with bosentan, a combined ETA/ETB receptor blocker, (n = 5 in each group).

2. On day 4 after BDL, serum bilirubin had increased to 226 ± 10 μmol/l (SEM) as compared with 6 ± 2 μmol/l in SO rats. Endogenous creatinine clearance, an index of glomerular filtration rate, was significantly reduced to 0.7 ± 0.1 ml min⁻¹ g⁻¹ of kidney weight after BDL as compared with 1.1 ± 0.1 ml min⁻¹ g⁻¹ of kidney weight after SO (P < 0.05). Bosentan prevented the decrease in glomerular filtration rate (1.0 ± 0.2 ml min⁻¹ g⁻¹ of kidney weight), as well as polyuria and defective concentrating ability, in BDL rats.

3. Plasma ET concentration on day 4 after surgery (28.2 ± 1.5 pmol/l) was higher (P < 0.01) in BDL than in SO rats (12.9 ± 1.5 pmol/l) and rose further in bosentan-treated BDL and SO rats (43.4 ± 5.1 compared with 21.9 ± 6.6 pmol/l). Urinary ET excretion was significantly higher in BDL rats than in SO rats (1.58 ± 0.22 compared with 1.28 ± 0.18 pmol 24 h⁻¹ 100 g⁻¹ of body weight; P < 0.05).

4. ET synthesis by glomeruli isolated from BDL rats was lower [81 ± 19 fmol h⁻¹ (mg of protein)⁻¹] than that from SO-rats [139 ± 28 fmol h⁻¹ (mg of protein)⁻¹; P < 0.05], whereas papillary ET synthesis was higher in BDL [10 ± 3 fmol h⁻¹ (mg of protein)⁻¹] than in SO rats [4 ± 1 fmol h⁻¹ (mg of protein)⁻¹; P < 0.05].

5. The results indicate that BDL is associated with increased plasma ET concentration and suppression of GFR. Enhanced renal inner medullary collecting-duct ET synthesis, which is reflected by increased urinary ET excretion, may reduce distal tubular water absorption in BDL rats. Increased circulating and renal papillary ET synthesis may thus contribute to renal dysfunction and predispose the kidney to acute renal failure in obstructive jaundice.

INTRODUCTION

One out of ten patients with obstructive jaundice may develop acute renal failure (ARF) after major surgery which is associated with high mortality [1–3]. Various haemodynamic and hormonal [2, 4–7], and humoral factors, e.g. bile constituents [8–10] and endotoxins [11–14], may contribute to circulatory shock and render the kidney susceptible to hypoxic damage [2] and ARF.

In animal models, such as acute or chronic bile duct-ligation (BDL), reduced renal perfusion and redistribution of renal blood flow [15–17], depression of glomerular filtration rate (GFR) [15, 17, 18] and of sodium excretion [16, 19], as well as disturbances in the concentrating and diluting ability [19–22] of the kidney, were found. In BDL rats, plasma concentrations of bilirubin, bile acids and creatinine [23, 24] reach their maximum between days 3 and 6 after BDL, and endogenous creatinine clearance, as a rough measure of GFR, is most profoundly depressed during this time period [15, 19, 20, 22]. On day 4 after BDL, other workers have reported increased urinary excretion of 6-keto-prostaglandin F₁α and thromboxane (TX) B₂ [25], whereas we previously found increased urinary TXB₂ but normal prostaglandin E₂ excretion on the sixth day after BDL [22]. We have also recently shown in rats with BDL that impaired renal function is associated with increased glomerular TX synthesis and urinary TX excretion, and that the depression of GFR is reversed by TX-receptor blockade [26]. Moreover, endothelin (ET), a potent renal vasoconstrictor that also causes water diuresis [27], has been implicated to play a role in ARF [28]. We therefore
speculated that enhanced renal ET synthesis may impair renal haemodynamic and tubular functions, especially renal concentrating ability, in obstructive jaundice.

Thus in the present study we investigated GFR and renal function in relation to the renal ET system, i.e. urinary ET excretion as compared with plasma ET, as well as ET synthesis by isolated renal glomeruli and papillae on day 4 after surgery in BDL rats as compared with SO rats. To further evaluate a potential renal action of ET after BDL we also studied the effects of the ETA/ETB receptor antagonist bosentan [29] on renal function after BDL.

MATERIAL AND METHODS
Experimental protocol

Studies were performed in 24 female Sprague-Dawley rats with a mean body weight of 244.6 ± 6.4 g (SEM) (range 205–265 g). The animals received a standard rat chow diet (Altromin®; Lage, Germany) and tap water ad libitum. The diet contains 19% protein, 9.9% lysine, 4% fat, 0.9% calcium, 0.7% phosphorus, 15% fibres and, per kg of diet, vitamins A, D3 and E, 15,000 IU, 600 IU and 75 mg, respectively, as well as 5 mg of copper. For adaptation, rats were placed into individual metabolic cages 8 days before the start of the experiments, which were performed according to the Declaration of Helsinki with the permission of the Governmental Animal Protection Committee. Rats were subdivided into four groups: sham-operated (SO) rats served as controls (n = 7); BDL rats (n = 7); SO rats (n = 5) and BDL rats (n = 5) who received bosentan, a combined ETA and ETB receptor blocker, after surgery.

For surgical procedures the animals were anaesthetized with methohexital® (brevimytal-Na; Lilly Co, Giessen, Germany), 45–65 mg/kg of body weight, intraperitoneally. After an upper abdominal incision the bile duct was prepared to a length of 1 cm and was cut between two firm ligatures. In SO rats the common bile duct was intact. The abdominal incision was then closed by single sutures with subsequent local application of 2% xylocaine gel (Astra Chemicals, Wedel, Germany). The animals were then returned to their metabolic cages.

Bosentan was administered by gastric tube at a dose of 10 mg/100 g of body weight once daily beginning immediately after surgery.

On the day before surgery and on day 4 after surgery, blood pressure was determined by tail-plethysmography; 24 h urine samples were collected and volumes were calculated gravimetrically. On day 4 after surgery, urine was collected during two consecutive 2 h periods. Desamino-8-D-arginine-vasopressin (d-DAVP), at a dose of 20 ng/kg of body weight, was then administered intraperitoneally and urine was again collected for two consecutive 2 h periods. After measurement of urinary osmolality urine samples were stored frozen at −20°C.

At the end of the experiments animals were anaesthetized with methohexital® as described above. After determining body weight, an abdominal incision was made and the animals were killed by collecting blood by aortic puncture. Kidneys were removed and weighed. After measurement of osmolality, plasma, serum and urine samples were stored frozen at −20°C.

Isolation and incubation of glomeruli and papillary tissue

After blood collection both kidneys were removed and immediately placed in ice-cold PBS (in mmol/l: 137 NaCl, 2.7 KCl, 8.1 Na2HPO4, 1.5 KH2PO4; pH 7.4). After removal of fat and fibrous tissue, kidney weight was determined.

The isolation of glomeruli was performed according to the method of Misra [30]. Kidney cortex was minced to paste-like consistency. The tissue in cold PBS buffer was then passed through a stainless-steel sieving system consisting of three sieves with meshes 150, 100 and 75 μm respectively. The procedure was repeated and the glomeruli were collected on the 75 μm mesh sieve. The glomeruli were then washed with PBS buffer and subsequently centrifuged for 5 min at 600 g at 4°C. The supernatant was removed and the glomeruli were suspended in Krebs–Ringer bicarbonate/glucose (KRB) buffer (in mmol/l: 150 NaCl, 4.7 KCl, 14 glucose, 1.8 KH2PO4, 1.8 MgSO4, 2.5 CaCl2, 25 NaHCO3). After centrifugation the supernatant was removed and the glomeruli were resuspended in 5 ml of KRB buffer. Aliquots of each 500 μl of the glomerular suspension containing 150–200 μg of protein were pipetted into polypropylene vials. Incubation for 60 min was performed in a 37°C water bath shaken at a frequency of 60 cycles/min, and samples were gassed with 95% O2/5% CO2. Incubation was stopped by placing the incubation tubes into ice-cold water. The tubes were then centrifuged for 10 min at 2000 g at 4°C. The supernatant was stored at −20°C until assayed. For blank values, aliquots from glomerular suspensions were placed in an ice-cold water bath before incubation at 37°C was started (see above). They were subsequently centrifuged for 10 min at 2000 g at 4°C and the supernatant was again stored at −20°C.

The two papillae of each animal were minced with razor blades into small pieces. They were then washed with PBS buffer and subsequently centrifuged for 5 min at 600 g at 4°C. The supernatant was removed and papillary tissue was resuspended in 5 ml of KRB buffer. Aliquots of each 500 μl of papillary tissue suspension, containing approximately 350 μg of protein, were pipetted into polypropylene vials. Incubation for 60 min was performed in the
same manner as described for glomeruli. Determination of ET and of protein, as well as calculations, were performed identically as for the glomeruli.

**Analytical methods**

ET concentrations in extracted plasma [31] and in unextracted urine were determined by RIA (ET-1,2 RIA; Amersham Buchler, Braunschweig, Germany). The antibody cross-reacts as follows: with ET-1 100%, ET-2 204%, ET-3 0.0024% and big ET-1 (porcine) 32.9%. Determination of ET concentrations in supernatants from incubates of glomeruli and papillae without prior extraction were determined by an ELISA specific for ET-1 (ET-1 ELISA; Amersham Buchler). Determination of ET-1 by ELISA in unextracted urine and supernatants of isolated glomeruli and papillary tissue resulted in values that were almost identical with those obtained by ET-1,2 RIA.

Protein concentration in aliquots of tissue suspensions after homogenization was determined according to the method of Lowry et al. [32]. Serum bilirubin concentration was determined by a conventional autoanalyser method. Concentrations of creatinine in serum and urine were measured after adsorption to Fuller's earth by the Jaffé reaction [33]. Serum and urine osmolalities were measured by freezing-point depression using a semi-automatic osmometer (Vogel; Giessen, Germany). Endogenous creatinine clearance, a rough measure of GFR, was calculated with the conventional formula and expressed as ml min⁻¹ g⁻¹ of kidney weight. Urinary ET excretion was expressed as pmol h⁻¹ 100 g⁻¹ of body weight. ET synthesis by isolated glomeruli and papillary tissue was calculated from the difference between total ET concentrations minus blank values before and after 60 min of incubation and was expressed as fmol of ET h⁻¹ (mg of protein⁻¹).

**Statistics**

For statistical evaluation of differences between groups, two-tailed Student's t-test and, when appropriate, Wilcoxon's signed rank test for paired and unpaired data, respectively, were used. Data are presented as means±SEM.

**RESULTS**

**Body and kidney weight, blood pressure and serum bilirubin and creatinine concentrations**

In SO and BDL rats body weight had decreased slightly but insignificantly on day 4 after surgery. It had decreased to a slightly greater extent in bosentan-treated rats. Kidney weight on day 4 after surgery was slightly lower in bosentan-treated rats (P<0.05) (Table 1).

Systolic blood pressure in SO and BDL rats was similar to pre-surgical values and was unaffected by bosentan (Table 1).

Serum bilirubin concentration had increased more than 30-fold after BDL without and with bosentan respectively (Table 1).

Serum creatinine concentrations had increased significantly on day 4 after surgery. Bosentan had no effect on serum creatinine concentration in SO rats but attenuated its increase in BDL rats (P<0.05) (Table 1).

**Renal function**

Endogenous creatinine clearance was significantly reduced on day 4 in BDL as compared with SO rats (P<0.01). Bosentan, administered daily after surgery, had no effect on creatinine clearance in SO rats, but maintained it at the normal level in BDL rats (Table 2 and Fig. 1).

Twenty-four hour urine volume had increased significantly in BDL rats after surgery (P<0.05). Bosentan had no effect on urine volume in SO rats but prevented polyuria after surgery in BDL rats (Table 2).

Urinary osmolality was similar in all groups before surgery (except for some slight but significant differences). On day 4 after surgery urinary osmolality was significantly (P<0.05) lower in BDL rats than in SO rats. After treatment with bosentan, urinary osmolality increased in BDL rats on day 4 after sur-

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**Table 1. Change in body weight as well as kidney weight, systolic blood pressure and serum bilirubin and creatinine concentrations on day 4 after sham operation or bile-duct ligation in vehicle- and bosentan (B)-treated rats.**

<table>
<thead>
<tr>
<th></th>
<th>SO (n = 7)</th>
<th>SO+B (n = 5)</th>
<th>BDL (n = 7)</th>
<th>BDL+B (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight post-</td>
<td>-3±2</td>
<td>-7±4</td>
<td>-7±5</td>
<td>-8±3</td>
</tr>
<tr>
<td>compared with pre-surgery (g)</td>
<td></td>
<td></td>
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<tr>
<td>Kidney weight (g)</td>
<td>1.68±0.03</td>
<td>1.45±0.03†</td>
<td>1.71±0.03</td>
<td>1.59±0.04†</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>112±2</td>
<td>111±2</td>
<td>110±2</td>
<td>108±2</td>
</tr>
<tr>
<td>Serum bilirubin (µmol l⁻¹)</td>
<td>6±2</td>
<td>8±1</td>
<td>226±10*</td>
<td>238±15*</td>
</tr>
<tr>
<td>Serum creatinine (µmol l⁻¹)</td>
<td>33±2</td>
<td>35±2</td>
<td>47±2*</td>
<td>42±2*††</td>
</tr>
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</table>
surgery to a similar level as did urine osmolality in bosentan-treated SO rats (Fig. 1 and Table 2).

With administration of d-DAVP on day 4 after surgery, urine osmolalities in BDL rats rose by 661 ± 124 mosm/kg in BDL rats as compared with 1012 ± 129 mosm/kg in SO rats (P < 0.05). This difference between BDL and SO rats was blunted by treatment with bosentan, which resulted in a d-DAVP-induced increase in urine osmolality of 655 ± 88 mosm/kg in BDL rats and of 720 ± 99 mosm/kg in SO rats respectively.

**Plasma ET concentration.** On day 4 after surgery, the plasma ET concentration was higher in BDL (28.2 ± 1.5 pmol/l) than in SO rats (12.9 ± 1.5 pmol/l); P < 0.01. It increased further in bosentan-treated BDL and SO rats to 43.4 ± 5.1 and 21.9 ± 6.6 pmol/l respectively; P < 0.05 (Fig. 2).

**Urinary ET excretion.** Urinary ET excretion had significantly increased on day 4 after surgery in BDL rats, but not in SO rats (P < 0.05). It rose further in bosentan-treated BDL rats (P < 0.05), but not in SO rats in whom it remained similar to that of untreated SO rats after surgery or to pre-surgical values of bosentan-treated BDL and SO rats (Table 2 and Fig. 3).

### Table 2. Endogenous creatinine clearance, urine volume, urinary osmolality and urinary ET excretion before and on day 4 after surgery, as well as the response of urine osmolality to d-DAVP administration after surgery, in vehicle- and bosentan (B)-treated rats. *P < 0.05 for BDL compared with SO rats; **P < 0.01 for BDL compared with SO rats; †P < 0.05 for bosentan-treated compared with untreated rats.

<table>
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<tr>
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<th>SO (n = 7)</th>
<th>SO+B (n = 5)</th>
<th>BDL (n = 7)</th>
<th>BDL+B (n = 5)</th>
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<tr>
<td>Creatinine clearance after surgery (ml min⁻¹ g⁻¹ of k.wt.)</td>
<td>1.1 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.7 ± 0.1**</td>
<td>1.0 ± 0.2</td>
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<tr>
<td>Urine volume (ml/24 h)</td>
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<tr>
<td>Before surgery</td>
<td>5.1 ± 0.4</td>
<td>5.8 ± 0.3</td>
<td>5.6 ± 0.4</td>
<td>6.2 ± 0.4</td>
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<tr>
<td>After surgery</td>
<td>6.4 ± 0.9</td>
<td>5.3 ± 0.4</td>
<td>8.6 ± 1.4*</td>
<td>4.0 ± 0.5</td>
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<td>Urine osmolality (mosm/kg)</td>
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<tr>
<td>Before surgery</td>
<td>1504 ± 71</td>
<td>1650 ± 187</td>
<td>1380 ± 69</td>
<td>1536 ± 158</td>
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<tr>
<td>After surgery</td>
<td>1293 ± 144</td>
<td>1762 ± 117†t</td>
<td>951 ± 110*</td>
<td>1890 ± 311†t</td>
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<tr>
<td>Response to d-DAVP after surgery</td>
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<tr>
<td>Before d-DAVP</td>
<td>1147 ± 158</td>
<td>1590 ± 177</td>
<td>936 ± 123</td>
<td>1518 ± 79*</td>
</tr>
<tr>
<td>After d-DAVP</td>
<td>2159 ± 202</td>
<td>2310 ± 133</td>
<td>1597 ± 121*</td>
<td>2173 ± 161*</td>
</tr>
<tr>
<td>Urinary ET excretion (pmol 24 h⁻¹ 100 g⁻¹ of b.wt.)</td>
<td>1.18 ± 0.12</td>
<td>1.23 ± 0.08</td>
<td>1.24 ± 0.10</td>
<td>1.20 ± 0.20</td>
</tr>
<tr>
<td>Before surgery</td>
<td>1.28 ± 0.18</td>
<td>1.46 ± 0.26</td>
<td>1.58 ± 0.22*</td>
<td>1.82 ± 0.50*</td>
</tr>
<tr>
<td>After surgery</td>
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**Glomerular and papillary ET synthesis**

**Glomerular ET synthesis.** On day 4 after surgery, glomeruli isolated from BDL rats showed an ET synthesis of 81 ± 22 fmol h⁻¹ (mg of protein)⁻¹, which was slightly but significantly (P < 0.05) lower than the ET synthesis of 142 ± 33 fmol h⁻¹ (mg of protein)⁻¹ in SO rats.
Papillary ET synthesis. Incubates of papillary tissue from BDL rats showed a significantly greater ET synthesis of $10.4 \pm 2.7$ fmol h$^{-1}$ (mg of protein)$^{-1}$ than did papillary tissue from SO rats with a rate of synthesis of $4.3 \pm 1.1$ fmol h$^{-1}$ (mg of protein)$^{-1}$; $P<0.05$ (Fig. 3).

DISCUSSION

It is well known from clinical and experimental findings that obstructive jaundice is accompanied by peripheral vasodilatation, which responds poorly to hormonal vasoconstrictors such as angiotensin II and noradrenaline [4, 5, 23, 25, 34, 35]; in contrast, the renal vasculature is constricted [15, 21]. Experimental studies on a potential role of catecholamines in BDL have so far led to equivocal results [18, 25, 35]. We had observed in rats with BDL that impaired renal function is associated with increased glomerular synthesis of the vasoconstrictor TX and increased urinary TX excretion, and that the depression of GFR is reversed by TX-receptor blockade [26]. In support of a role for TX, we have also observed that TX may have a pathogenetic role in the early phase of ischaemic ARF [36].

More recently, ET, a potent endothelium-derived vasoconstrictor [37] that also antagonizes the tubular action of arginine vasopressin [38], has been implicated to play a role in acute [28] and chronic renal failure [31]. We therefore speculated that enhanced renal ET synthesis may impair renal haemodynamic and tubular functions, especially renal concentrating ability, in obstructive jaundice.

In the present study we confirmed our own previous observations [22], and those of other workers [15, 25, 34, 35], of a significant decrease in GFR. Various investigators also found a decrease in renal (cortical) blood flow [15, 21] during the first 2 weeks after BDL, which was more pronounced in outer cortical than in juxtamedullary nephrons [15, 18, 39]; 2 weeks after BDL, GFR seems to be restored to normal [21, 39].

To explore further the role of ET in renal dysfunction after BDL, we investigated plasma ET concentration, urinary ET excretion and ET synthesis by isolated glomeruli and papillary tissue in rats, as well as the action of the ETA/ETB receptor-antagonist bosentan [29], on renal function after BDL. We found that plasma concentrations of ET and urinary ET excretion are increased in rats on day 4 after BDL. Elevated plasma ET may represent spill-over of excessive vascular ET synthesis. Moreover, increased circulating ET may contribute to the reduction in GFR after BDL, and this is supported by the ability of bosentan to completely restore GFR (see below), despite the fact that this receptor blocker further increased plasma ET concentration, as previously reported [40], and urinary ET excretion. It is not clear why ET production by isolated glomeruli was decreased after BDL in the presence of high levels of circulating ET; however, a similar inverse relation of regional ET synthesis to circulating ET has been reported previously [41]. Increased urinary ET excretion may reflect the enhanced ET production by renal papillary tissue, probably by distal tubular epithelial cells [42], that we observed after BDL, although flow-dependent increases in urinary ET excretion cannot be excluded [42].

As we [22] and others [19–21, 39] have observed previously, in the present study BDL was associated with an increase in urine flow and decreased urine osmolality. Defective renal concentrating ability [21] may in part result from the diuretic action of hyperbilirubinaemia [43], the diuretic [44, 45] and sodium transport inhibiting actions of bile acids [46–48] or the redistribution of intrarenal blood flow, with preferential perfusion of juxtamedullary nephrons [15, 39] and subsequent wash-out of medullary solutes. We found previously that TXA$_2$/prostaglandin H$_2$ receptor blockade resulted in further urine dilution [26], which agrees with the finding that TX agonists promote chloride absorption in Henle's loop [49] and thereby may enhance urine concentration.

In the present study, treatment of BDL rats with bosentan completely restored GFR as well as spontaneous renal water absorption, with increased 24 h urine osmolality in both SO and BDL rats. With bosentan, the renal concentrating response to d-DAVP also became similar in BDL and SO rats. This is in agreement with the concept that ET at the inner medullary collecting duct level attenuates the cellular response to arginine vasopressin by suppression of cAMP synthesis in a short-loop auto- or
paracrine fashion [38, 42, 50]. It is also compatible with the notion that ET, via ET₆ receptors, may induce inner medullary vasodilatation [51], resulting in medullary wash-out. A diuretic action of ET in the rat, however, can be demonstrated only if GFR is not seriously compromised [27]. Since this effect was not observed in man [52], it may be species specific. Taken together, in the present study we found that rats after 4 days of BDL reveal a marked depression of GFR and a polycydrhia, which is due to a defective renal concentrating ability. This was accompanied by an increase in plasma ET concentration and in urinary ET excretion, the latter probably reflecting the observed increase in papillary ET synthesis. Both the impaired GFR and the defective renal concentrating ability were almost restored to normal by treatment with the ET receptor-antagonist bosentan. We therefore conclude that, in experimental obstructive jaundice, increased circulating ET probably leads to renal arterial vasoconstriction, resulting in a decrease in GFR. Enhanced papillary ET synthesis may be assumed to contribute to the defective renal concentrating ability.

Our previous and present results suggest that some bile constituents, retained after BDL, enhance vascular and renal papillary ET release and stimulate renal TX synthesis. To elucidate the differential roles of the renal TX system and the circulating and renal ET systems in obstructive jaundice further detailed experimental studies are required. With respect to our previous finding that ET is partly protected by TX receptor blockade, and our present observation of a similar effect of bosentan, it is worth referring to recent results that we obtained by micropuncture technique in the dog kidney. We found that intrarenal arterial administration of ET-1 causes pre- and post-glomerular vasoconstriction and a decrease in the ultrafiltration coefficient, Kf, which are probably mediated largely by other vasoconstrictor hormones or autacoids such as TX [53]. Whatever the exact mechanisms may be, our results suggest that, under experimental conditions, increased vascular and renal glomerular TX synthesis, as well as increased circulating and renal papillary ET production, i.e. ET synthesis by inner medullary collecting-duct cells, contribute to the suppression of GFR and distal tubular dysfunction after BDL in the rat. These changes in autacoid production, with the subsequent renal functional alterations, may also predispose the jaundiced human kidney to ARF. Therefore, antagonists of TX and especially of ET receptors may not only be protective in experimental BDL but may also serve as promising tools for therapeutic interventions in patients with obstructive jaundice.

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