Regular Article

Elevated Systemic Elimination of Cimetidine in Rats with Acute Biliary Obstruction: The Role of Renal Organic Cation Transporter OCT2

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Summary: Renal tubular secretion of cationic drugs is dominated by two classes of organic cation transporters, OCT2/SLC22A2 and MATE1/SLC47A1, localized to the basolateral and brush-border membranes of the renal tubular epithelial cells, respectively. However, little is known about the expression and function of these transporters in acute cholestasis. Systemic clearance of cimetidine was significantly higher in rats with bile duct ligation (BDL) for 24 hours than in sham-operated rats, with no significant changes in the volume of distribution between the groups. In addition, net tubular secretory clearance of cimetidine was significantly higher in the BDL rats compared with the sham rats, with no significant changes in the glomerular filtration rate. Moreover, the renal tissue-to-plasma concentration ratio of cimetidine was elevated in BDL rats, although the renal tissue-to-urine clearance ratio of cimetidine was not different between the two groups. The expression level of basolateral organic cation transporter rOCT2 protein in the kidney cortex was markedly higher in BDL rats than that in the sham rats, but that of H+/organic cation antiporter rMATE1 protein in the brush-border membranes was not significantly different between the two groups. These results demonstrate that the renal tubular secretion of cimetidine was increased by acute cholestasis, and this increase was attributable to elevated expression levels of rOCT2 but not of rMATE1 in the rat.

Keywords: bile duct ligation; organic cation transporter 2; multidrug and toxin extrusion 1; tubular secretion; cimetidine

Introduction

The kidney is a major organ mediating the elimination of various therapeutic agents and xenobiotics, of which some are positively charged. Generally, net urinary excretion of cationic drugs in the kidney is the consequence of three physiological processes: glomerular filtration, tubular secretion, and tubular reabsorption.

Organic cation transporter 2 (OCT2/SLC22A2), which was identified by Okuda et al. in 1996, is the second member of the OCT family and has the highest expression levels among this family in the kidney.1-3 OCT2 is responsible for the entry of various organic cations, such as cimetidine, metformin, cisplatin, and guanidine, from the blood into the proximal tubular epithelial cells across basolateral membranes,1,4,5 whereas, at the brush-border membranes, the H+/organic cation antiporter (MATE1/SLC47A1, MATE2-K/SLC47A2) mediates the extrusion of these organic cations from the cells into the tubular lumen using the transmembrane H+ gradient as a driving force.6,7 Therefore, expression levels and/or functions of these transporters could regulate tubular secretion of cationic drugs, which could thereby result in the unexpected pharmacodynamics of cationic drugs.

Cimetidine is a H2 receptor antagonist used for the treatment of peptic ulcers and related disorders and is eliminated mainly by renal excretion (in humans, ~48% by 24 hours, in rats, ~70% by 72 hours after oral inges-
Cimetidine undergoes extensive tubular secretion at a 2.8-fold higher rate than glomerular filtration.\(^{10}\) In chronic renal failure rat models, such as 5/6 nephrectomized rats or hyperuricemic rats, tubular secretion of cimetidine is decreased in accordance with the decreased expression level of rOCT2,\(^{11,12}\) but there are few reports concerning the alteration of cimetidine pharmacokinetics in animal models with hepatic failure.

Obstructive jaundice is defined as retention of bile and its components after extrahepatic or intrahepatic bile duct obstruction. Extrahepatic cholestasis refers to obstruction of the large bile ducts outside the liver due to, for instance, gallstones. Moreover, cholestasis results in intrahepatic accumulation of cytotoxic bile acids, which leads to liver injury. Although systemic clearance of cimetidine is affected in patients with cirrhosis, no consistent change in cimetidine clearance in patients with hepatic failure has been suggested to date.\(^{13,14}\) In addition, the effect of cholestasis on cimetidine clearance has not yet been reported.

Recently, Tanaka et al. reported that in a jaundice rat model with bile duct ligation (BDL) for 1 and 3 days, the level of multidrug resistance-associated protein 2 localized to the brush-border membranes in the renal proximal tubules was increased in accordance with the concomitant elevation of renal p-aminohippurate (PAH) clearance.\(^{15}\) In addition, Brandoni et al. showed that in acute cholestasis rats with BDL for 21 hours, the expression level of organic anion transporter 1 (OAT1/SLC22A6) protein in the kidney was increased in accordance with increased systemic clearance of PAH, although that of OAT3/SLC22A8 in the kidney was unchanged.\(^{16}\) On the other hand, at 3 days after BDL, the expression level of OAT1 protein was decreased, whereas that of OAT3 was increased in rat kidney.\(^{17}\) However, the expression levels and functions of renal OCT2 as a result of obstructive jaundice have not been clarified. The purpose of this study was to clarify the effects of acute cholestasis on the expression levels and functions of OCT2 in the kidney.

**Methods**

**Materials:** Cimetidine and pentobarbital were obtained from Nacalai Tesque (Kyoto, Japan) and Dainippon Sumitomo Pharma Co. (Osaka, Japan), respectively. All other chemicals used were of the highest purity available.

**Experimental animals:** All animal experiments were performed in accordance with the Guidelines for Animal Experiments of Mie University. Male Wistar rats aged 9–11 weeks were purchased from SLC Animal Research Laboratories (Shizuoka, Japan). For surgical procedures, the animals were anesthetized with sodium pentobarbital. After upper abdominal incision under sterile conditions, the common bile duct was isolated and double-ligated close to the liver hilus immediately below the bifurcation and cut between the ligatures (BDL group).\(^{18}\) Rats that underwent the operation without ligation of the bile duct were used as controls (sham). The abdominal incision was then closed by single sutures. Animals were allowed free access to a standard laboratory chow and tap water and were housed in an environment at constant temperature and humidity with regular light cycles (12 h) during the experiments.

**Biochemical determinations:** Blood was withdrawn from the femoral artery before administering cimetidine to sham and BDL animals. Plasma was separated by centrifugation (10,600 × g, 10 min) and then subjected to assays for total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) as parameters indicative of hepatic function. Renal function was assessed on the basis of plasma creatinine levels. The biochemical analyses were determined using a kit obtained from Wako Pure Chemical Industries (Osaka, Japan). Plasma testosterone level was measured with an enzyme immunoassay kit (Cayman Chemical Co., Ann Arbor, MI, USA).

**In vivo systemic clearance experiments:** At 24 hours after surgery, sham and BDL rats were anesthetized with sodium pentobarbital (50 mg/kg i.p.). The femoral artery and vein were both catheterized to obtain blood samples from the artery and to administer test compounds into the vein, respectively, with polyethylene tubing (SP45, Natsume Seisakusho, Tokyo, Japan). Thereafter, in the experiment for cimetidine clearance, doses of 8 mg/kg of cimetidine were administered and blood samples were collected 0–240 min after the administration of cimetidine solution. An equivalent volume of saline solution was infused to restore the amount extracted in the blood samples. The blood collected was centrifuged at 10,600 × g for 10 min, and the extracted plasma samples were stored frozen at −80°C until analysis. Pharmacokinetic parameters such as area under the plasma concentration-time curve (AUC) and systemic clearance (CLtot) were calculated from cimetidine plasma concentrations. Moreover, the plasma concentration-time curves for cimetidine were fitted to a triexponential curve using WAPAS software (an automated pharmacokinetic analysis system).\(^{19}\) The choice of the best fit was based on Akaike’s information criterion. The elimination rate from the central compartment (Kel) and the total volume of distribution (Vd) were calculated according to standard procedures for compartmental analysis.

**In vivo renal clearance experiments:** In vivo renal clearance experiments were performed as described previously.\(^{12}\) Sham and BDL rats were anesthetized with sodium pentobarbital, and the femoral artery, vein, and bladder were cannulated with polyethylene tubing SP45. Blank urine was collected for 10 min and blank blood was collected. Thereafter, in the experiment for cimet-
The concentrations of cimetidine were determined by ultrafiltration using YM-10 columns (MCKON, Millipore, Billerica, MA, USA). Renal secretory clearance was calculated using the equation CLTS = CLR − fu × GFR, where CLTS is tubular secretory clearance, CLR is renal clearance, and fu is the unbound fraction. Renal luminal efflux clearance was calculated using the equation: Luminal efflux clearance (ml/min) = Urinary excreted amount (mg)/Renal tissue AUC (mg min/kg).

**Determination of cimetidine in the plasma, urine, and kidney:** The concentrations of cimetidine in the plasma, urine, and kidney were determined according to the methods reported previously with slight modifications.20,21) An LC-20AD HPLC apparatus (Shimadzu, Kyoto, Japan) equipped with a UV spectrophotometric detector (SPD-20A; Shimadzu) adjusted to 235 nm for cimetidine and an integrator (Chromatopac C-R8A; Shimadzu) were used. The stationary phase was a reversed-phase Chemcobond 5-ODS-H column (4.0 × 150 mm, Chemco Scientific, Osaka, Japan). The flow rate was 1.0 ml/min and the column temperature was maintained at 40°C. The mobile phase consisted of 95% phosphate buffer (50 mM, pH 5.5) and 5% acetonitrile.

**Western blotting analyses:** Crude membrane fractions were prepared from the kidney of sham and BDL rats as described previously with slight modifications.23) The crude plasma membrane fractions were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred onto polyvinylidene difluoride membranes by semi-dry electroblotting. The blots were blocked with 5% non-fat milk and 5% bovine serum albumin in phosphate-buffered saline (PBS, 137 mM NaCl, 3 mM KCl, 8 mM Na2HPO4, 1 M KH2PO4, 12 mM K2HPO4, pH 7.5) containing 0.5% Tween 20 (PBS-T) and incubated overnight at 4°C with polyclonal antibodies raised against rOCT1, rOCT2, rMATE1 (a generous gift from Prof. Ken-ichi Inui, Department of Pharmacy, Kyoto University Hospital, Japan), and villin (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA). The blots were washed three times with PBS-T, and the bound antibody was detected on X-ray film by enhanced chemiluminescence with horseradish peroxidase-conjugated secondary antibodies and cyclic diacylhydrazides (GE Healthcare, Buckinghamshire, UK). The density of bands was determined using a lumino image analyzer (LAS1000 plus, Fujifilm, Tokyo Japan) and immunoreactive bands were scanned and semiquantified using Image J 1.38 software (National Institutes of Health, Bethesda, MD, USA).

**Statistical analyses:** The statistical significance of differences between mean values was calculated using the non-paired t-test.

**Results**

**Plasma biochemical parameters in sham and BDL rats:** First, plasma biochemical parameters were evaluated in sham and BDL rats. The total bilirubin levels in BDL rats (2.90 ± 0.31 mg/dl) were 22-fold higher than those observed in sham rats (0.13 ± 0.05 mg/dl). The levels of AST and ALT were also much higher in BDL rats than in sham rats (77.8 ± 20.3 IU/l and 364.4 ± 104.4 IU/l for AST, 25.9 ± 4.1 IU/l and 276.7 ± 94.6 IU/l for ALT, for sham and BDL rats, respectively). The findings for the plasma biochemical parameters in BDL rats suggested the establishment of severe liver damage associated with cholestasis. In contrast to the parameters indicating hepatic functions, there was no significant difference in the plasma creatinine levels between sham and BDL rats (0.93 ± 0.04 and 0.95 ± 0.05 mg/dl for sham and BDL rats, respectively). (Table 1).

**Effect of BDL on the pharmacokinetics of cimetidine:** The mean plasma concentration-time profiles for cimetidine in sham and BDL rats are shown in Figure 1. The BDL rats showed significantly lower AUC values for cimetidine (188.7 ± 24.7 and 125.8 ± 14.3 µg min/ml for sham and BDL rats, respectively) and a significantly higher systemic clearance (0.043 ± 0.005 and 0.064 ± 0.007 l/min/kg for sham and BDL rats, respectively) compared with sham rats. Moreover, the plasma concentration-time curve was fitted best by a triexponential equation. According to the results of these analyses, elimination of cimetidine from the central compartment was significantly higher in BDL rats than that in sham rats (0.053 ± 0.005 min⁻¹ and 0.090 ± 0.002 min⁻¹ for sham and BDL rats, respectively). On the other hand, Vd

**Table 1. Plasma biochemical parameters in sham and BDL rats**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham (µg/ml)</th>
<th>BDL (µg/ml)</th>
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<tbody>
<tr>
<td>T-Bil</td>
<td>0.13 ± 0.05</td>
<td>2.90 ± 0.31*</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>77.8 ± 20.3</td>
<td>364.4 ± 104.4*</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>25.9 ± 4.1</td>
<td>276.7 ± 94.6*</td>
</tr>
<tr>
<td>Cre (mg/dl)</td>
<td>0.93 ± 0.04</td>
<td>0.95 ± 0.05</td>
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</table>

Results are expressed as mean ± S.D. of sham (n=5) and BDL (n=4) rats. *p<0.01 vs sham T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cre, plasma creatinine
was not different between the sham and BDL groups (Table 2).

**Effect of BDL on renal clearance of cimetidine:**
Next, renal clearance of cimetidine was evaluated and compared between sham and BDL rats. Table 3 shows the renal handling of cimetidine after intravenous infusion in sham and BDL rats. The unbound fraction of cimetidine (0.70 ± 0.04 and 0.75 ± 0.04 for sham and BDL rats, respectively) and glomerular filtration rate of unbound cimetidine (8.67 ± 0.38 and 8.48 ± 0.60 ml/min/kg for sham and BDL rats, respectively) were not different between sham and BDL rats. In contrast, the renal clearance of cimetidine (23.2 ± 0.60 and 27.3 ± 0.70 ml/min/kg for sham and BDL rats, respectively) and net renal secretory clearance (17.2 ± 0.57 and 21.0 ± 0.72 ml/min/kg for sham and BDL rats, respectively) of cimetidine were significantly higher in BDL rats than in sham rats.

**Effect of BDL on renal tissue distribution and renal tissue-to-plasma concentration ratio of cimetidine:**
To obtain the relative contributions of membrane transport at the basolateral and brush-border membranes on the increased tubular secretion of cimetidine, the renal tissue-to-plasma concentration ratio as well as renal tissue-to-urine clearance ratio of cimetidine was assessed in both sham and BDL rats. As a result, the renal tissue-to-plasma concentration ratio was markedly increased by

![Fig. 1. Time course of the plasma concentration of cimetidine after intravenous administration at a dose of 8 mg/kg in sham (○) and BDL rats (●). Each point represents mean ± S.D. of five (sham) and four (BDL) rats. *p < 0.05 vs sham rats.](image)

**Table 2. Pharmacokinetic parameters of cimetidine after intravenous administration in sham and BDL rats**

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>BDL</th>
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<tbody>
<tr>
<td>AUC (µg·min/ml)</td>
<td>188.7 ± 24.7</td>
<td>125.8 ± 14.3**</td>
</tr>
<tr>
<td>CLtot (l/min/kg)</td>
<td>0.043 ± 0.005</td>
<td>0.064 ± 0.007**</td>
</tr>
<tr>
<td>Kel (min⁻¹)</td>
<td>0.053 ± 0.005</td>
<td>0.090 ± 0.002***</td>
</tr>
<tr>
<td>Vd (µl/kg)</td>
<td>924.0 ± 61.6</td>
<td>863.0 ± 102.3</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± S.D. of sham (n = 5) and BDL (n = 4) rats. **p < 0.01, ***p < 0.001 vs sham
AUC, area under the concentration-time curve; CLtot, systemic clearance; Kel, elimination constant from the central compartment of a 3-compartment model; Vd, total volume of distribution

**Table 3. Renal and tubular secretory clearances of cimetidine in sham and BDL rats**

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>BDL</th>
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<tr>
<td>GFR (ml/min/kg)</td>
<td>8.67 ± 0.38</td>
<td>8.48 ± 0.60</td>
</tr>
<tr>
<td>fu</td>
<td>0.70 ± 0.04</td>
<td>0.75 ± 0.04</td>
</tr>
<tr>
<td>fu·GFR (ml/min/kg)</td>
<td>6.07 ± 0.27</td>
<td>6.34 ± 0.50</td>
</tr>
<tr>
<td>Clu (ml/min/kg)</td>
<td>23.2 ± 0.60</td>
<td>27.3 ± 0.70**</td>
</tr>
<tr>
<td>Clts (ml/min/kg)</td>
<td>17.2 ± 0.57</td>
<td>21.0 ± 0.72**</td>
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Results are expressed as mean ± S.D. of five rats. **p < 0.01 vs sham
GFR, glomerular filtration rate (measured by inulin clearance); fu, unbound fraction; Clu, renal clearance; Clts, tubular secretory clearance
Clts = Clu − fu × GFR

![Fig. 2. Renal tissue-to-plasma concentration ratio (A) and renal luminal efflux clearance (B) of cimetidine in sham (○) and BDL (●) rats. Luminal efflux clearance (ml/min): urinary excreted amount (mg)/renal tissue AUC (mg·min/ml). Results are expressed as mean ± S.D. Each point represents mean ± S.D. of six rats. *p < 0.05 vs sham rats.](image)
BDL (Fig. 2A; 1.19 ± 0.31 and 1.77 ± 0.36 for sham and BDL rats, respectively), whereas luminal efflux clearance was not different between the two groups (Fig. 2B; 2.64 ± 0.49 and 2.13 ± 0.47 ml/min for sham and BDL rats, respectively).

Expression levels of rOCT1, rOCT2, and rMATE1 in sham and BDL rats: To assess the molecular mechanisms responsible for the increased renal secretory clearance of cimetidine in BDL rats, the relative expression levels of renal organic cation transporters rOCT1, rOCT2, and rMATE1 in the crude plasma membranes isolated from kidney cortex were assessed by western blotting. As shown in Figs. 3A and 3D, the expression levels of rOCT2 in the renal cortex in BDL rats were 1.8-fold higher than those in sham rats. In contrast to rOCT2, the expression levels of rOCT1 in BDL rats were significantly lower than those of sham rats (Figs. 3B and 3D). Moreover, the expression levels of rMATE1 in the brush-border membranes of kidney cortex were not different between sham and BDL rats (Figs. 3C and 3D). The expression levels of villin were not different between sham and BDL rats in each experiment (Figs. 3A–D).

Plasma levels of testosterone in sham and BDL rats: Finally, the plasma testosterone levels were measured in the sham and BDL rats. As shown in Table 4, there was no significant difference in the plasma testosterone levels between sham and BDL rats (2.93 ± 0.64 and 2.48 ± 0.46 ng/ml for sham and BDL rats, respectively).

Discussion

In patients with hepatic injury caused by cholestasis, it has been reported that dose adjustments are required for some drugs because of altered pharmacokinetics and/or pharmacodynamics. Although the structures, tissue distributions, and functions of various drug transporters regulating pharmacokinetics have been clarified by studies performed in recent years, the significance of drug transporters in various disease states has not been fully elucidated. In the clinical setting, it has been reported that systemic and renal clearance of cimetidine is altered in cases of hepatic failure, but no consistent changes in the pharmacokinetics of cimetidine in cases of hepatic failure have been suggested to date. Moreover, alterations in the expression and functions of renal organic cation transporters in acute cholestasis have not been reported.

In the present study, the AUC of cimetidine in BDL rats was significantly lower than that of sham rats, and systemic clearance of cimetidine was markedly higher in BDL rats than sham rats (Fig. 1). Because the apparently decreased AUC of plasma cimetidine could be caused by increased systemic elimination of cimetidine, by increased Vd of cimetidine, or by both, the plasma concentration-time curve of cimetidine was analyzed further using a triexponential equation. Consequently, it was found that the elimination of cimetidine from the central compartment was markedly increased in BDL rats, although there was no significant difference in the Vd of cimetidine between sham and BDL rats (Table 2). Moreover, symptoms of edema or abnormal gain of body weight were not observed in BDL rats (data not shown), suggesting that the increased apparent elimination in BDL rats was due to increased systemic clearance rather than increased Vd of cimetidine.

It is known that about 70% of cimetidine administered orally is excreted from the kidney in rats. In the kidney, OCT2 and MATE1 play key roles in tubular secretion of cimetidine at the basolateral and brush-border mem-

Table 4. Plasma testosterone concentration of sham and BDL rats

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<th>Sham</th>
<th>BDL</th>
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<tr>
<td>Plasma testosterone levels (ng/ml)</td>
<td>2.93 ± 0.64</td>
<td>2.48 ± 0.46</td>
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Results are expressed as mean ± S.E. of six rats.
branes, respectively.\textsuperscript{25,26} In addition, there is no report suggesting expression of MATE2-K ortholog in the rat kidney. Because serum creatinine levels were not different between sham and BDL rats (Table 1) and the unbound fraction of cimetidine was not significantly different between the two groups, it was deduced that increased cimetidine clearance in BDL rats was attributable to increased tubular secretion rather than increased glomerular filtration rate. In order to confirm this hypothesis, renal tubular secretion and glomerular filtration rate of cimetidine were evaluated using an in vivo renal clearance method in sham and BDL rats. Because the glomerular filtration rate of cimetidine in BDL rats was not different from that in sham rats, it was suggested more strongly that increased systemic clearance of cimetidine by BDL was attributable to elevated tubular secretion of cimetidine in the kidney (Table 3). Furthermore, tubular reabsorption of cimetidine should be small in the in vivo renal clearance experiments, because the experiments were carried out under diuretic conditions using constant intravenous infusion of mannitol.

In the present study, the expression levels of rMATE1 in the kidney cortex were not different between sham and BDL rats (Fig. 3C), which was consistent with the results that efflux clearance of cimetidine across brush-border membranes was not different between sham and BDL rats (Fig. 2B). In contrast, the renal tissue-to-plasma concentration ratio of cimetidine was markedly higher in BDL rats than in sham rats (Fig. 2A), suggesting that the elevated tubular secretion of cimetidine was due to elevated tissue uptake clearance of cimetidine across the basolateral membranes. In the rat kidney, both rOCT1 and rOCT2 are expressed at the basolateral membranes of renal tubules,\textsuperscript{4,25} whereas hOCT2 is the only major organic cation transporter in the basolateral membranes of the human kidney,\textsuperscript{21} showing species-related differences between rats and humans. In the present study, the expression levels of rOCT2 in the kidney cortex were markedly higher in BDL rats than in sham rats (Fig. 3A), although the expression levels of rOCT1 in the kidney cortex were significantly lower in BDL rats than those in sham rats (Fig. 3B). It has been reported that the expression levels of rOCT2 are much higher than those of rOCT1 in the rat kidney.\textsuperscript{11} In addition, rOCT2 is responsible for the decreased renal clearances of cimetidine in the rats with various kidney diseases.\textsuperscript{11,12} It is known that cimetidine is recognized by rOAT3 in addition to rOCT2, although rOAT3 shows lower affinity for cimetidine than rOCT2.\textsuperscript{28} It has also been reported that expression levels of OAT3 protein in the kidney of rats at 21 hours after BDL did not change significantly compared with sham rats,\textsuperscript{16,17} suggesting that the elevated tubular secretion of cimetidine is attributable mostly to the increased expression levels of rOCT2.

Jin et al. reported that the expression levels of rOCT2 in the kidney were lower in rats with ethynylestradiol-induced cholestasis than in non-treated control rats.\textsuperscript{29} They also suggested that serum testosterone levels were significantly lower in ethynylestradiol-cholestatic rats than in control rats, which is consistent with a previous finding that estradiol downregulates renal rOCT2 expression.\textsuperscript{30} In the present study, rOCT2 levels in the kidney were higher in rats with BDL after 24-hours, suggesting an apparent discrepancy with the results by Jin et al. In the present study, plasma testosterone levels were not different between sham and BDL rats (Table 4). Therefore, it is likely that the elevated expression level of rOCT2 in BDL rats was mediated by a distinct mechanism(s) other than the androgen receptor. The mechanisms underlying the increased expression levels of rOCT2 as well as decreased expression levels of rOCT1 remain to be clarified.

In summary, the present study clarified for the first time that the tubular secretion of cimetidine is increased after BDL for 24 hours, and that this change is attributable to the elevated expression levels of rOCT2, but not of rMATE1. These results should provide useful information for the analysis and prediction of renal clearance of cationic drugs.

References


