Altered Pharmacokinetics of Cationic Drugs Caused by Down-Regulation of Renal Rat Organic Cation Transporter 2 (Slc22a2) and Rat Multidrug and Toxin Extrusion 1 (Slc47a1) in Ischemia/Reperfusion-Induced Acute Kidney Injury

Takanobu Matsuzaki, Takafuli Morisaki, Wakako Sugimoto, Koji Yokoo, Daisuke Sato, Hiroshi Nonoguchi, Kimio Tomita, Tomohiro Terada, Ken-ichi Inui, Akinobu Hamada, and Hideyuki Saito

Department of Pharmacy, Kumamoto University Hospital, Kumamoto, Japan (T.Ma., T.Mo., W.S., K.Y., D.S., A.H., H.S.); Department of Nephrology, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan (H.N., K.T.); and Department of Pharmacy, Kyoto University Hospital, Kyoto, Japan (T.T., K.I.)

Received November 21, 2007; accepted January 2, 2008

ABSTRACT:

In the proximal tubules of rat (r) kidney, the polycospecific organic cation transporters (OCTs), rOCT1 and rOCT2, mediate the basolateral uptake of various organic cations, including many drugs, toxins, and endogenous compounds, and the apical type of H+/organic cation antiporter, rat multidrug and toxin extrusion 1 (rMATE1), mediate the efflux of organic cations. Renal clearances of H2 receptor antagonists, including famotidine, were reported to be decreased in patients with kidney disease. Therefore, acute kidney injury (AKI) could influence renal excretion and disposition of organic cations accompanied by the regulation of organic cation transporters. The aim of this study was to investigate the pharmacokinetic alteration of cationic drugs and the expression of tubular organic cation transporters, rOCT1, rOCT2, and rMATE1, in ischemia/reperfusion (I/R)-induced AKI rats. I/R-induced AKI increased the plasma concentration of i.v. administrated famotidine, a substrate for rOCT1, rOCT2, or tetraethylammonium (TEA), a substrate for rOCT1, rOCT2, and rMATE1. The areas under the plasma concentration curves for famotidine and TEA were 2- and 6-fold higher in I/R rats than in sham-operated rats, respectively. The accumulation of TEA into renal slices was significantly decreased, suggesting that organic cation transport activity at the basolateral membranes was reduced in I/R rat kidney. The protein expressions of basolateral rOCT2 and luminal rMATE1 were down-regulated in I/R rat kidneys. These data suggest that the urinary secretion of cationic drugs via epithelial organic cation transporters is decreased in AKI.

The kidney mediates urinary excretion of a wide variety of xenobiotics, including drugs, toxins, and endogenous compounds. In renal proximal tubules, several directional organic solute transport systems facilitate active secretion of a wide range of exogenous and endogenous organic ions (Pritchard and Miller, 1996; Inui et al., 2000). Transport proteins for organic anions and cations localized specifically at the apical or basolateral membranes of the proximal tubular cells are responsible for urinary secretion of diverse drugs (Sweet and Pritchard, 1999; Inui et al., 2000; Sekine et al., 2000). The structures and functions of Slc22a gene family members of organic anion transporters (OATs) and organic cation transporters (OCTs), which mediate transepithelial transport of various organic anions and cations, have been characterized (Sweet and Pritchard, 1999; Inui et al., 2000; Sekine et al., 2000). rOAT1 (Slc22a6) and rOAT3 (Slc22a8) appear to mediate organic anion/α-ketoglutarate exchange at the basolateral membrane of the proximal tubules, including various organic anions (Sekine et al., 1997; Sweet and Pritchard, 1999; Tojo et al., 1999; Cha et al., 2001). On the other hand, rOCT1 (Slc22a1) and rOCT2 (Slc22a2) were reported to be driven by inside-negative membrane potential (Busch et al., 1996; Okuda et al., 1996), mediating basolateral uptake of diverse organic cations such as tetraethylammonium (TEA) and the H+ receptor antagonist cimetidine (Urakami et al., 1999; Cha et al., 2001). The H+/organic cation antiporter in renal brush-border membranes mediates active extrusion of cationic drugs or toxins out of renal tubular cells (Ullrich, 1997). The oppositely directed H+ gradient was demonstrated to be a driving force for the transport of organic cations such as TEA, a prototype substrate (Takano et al., 1999). More recently, the apical type of H+/organic cation antiporter, rat multidrug and toxin extrusion 1 (rMATE1/Scl47a1), has been identified and functionally characterized (Ohta et al., 2006; Terada et al., 2001).

This work was supported in part by Grant-in-Aid for Scientific Research (B) 17390158 from the Scientific Fund of the Ministry of Education, Science, and Culture of Japan.

Article, publication date, and citation information can be found at http://dmd.aspetjournals.org.


ABBREVIATIONS: OAT, organic anion transporter; OCT, organic cation transporter; r, rat; TEA, tetraethylammonium; MATE, multidrug and toxin extrusion; AKI, acute kidney injury; I/R, ischemia/reperfusion; h, human; BUN, blood urea nitrogen; SCr, serum creatinine; HPLC, high performance liquid chromatography; AUC, area under the plasma concentration curve; PCR, polymerase chain reaction; NHE, Na+/H+ exchanger.
luminal rMATE1 in association with AKI. In the present study, we hypothesized that decreased renal excretion of famotidine in patients with renal diseases have a great impact on renal clearance of their substrates. Acute kidney injury (AKI) caused by ischemia/reperfusion (I/R) is a critical syndrome associated with high mortality in humans (Thadhani et al., 1996; Star, 1998; Schrier et al., 2004). I/R-induced AKI is evoked by a complicated interaction among renal hemodynamics, inflammatory cytokines, and tubular cell damages (Bonventre and Weinberg, 2003). AKI is characterized principally by tubular dysfunction with impaired sodium and water reabsorption, which are associated with the shedding and excretion of renal brush-border membranes and epithelial tubule cells into the urine (Thadhani et al., 1996). After I/R, morphological changes occur in the proximal tubules, including loss of polarity, loss of the brush border, and redistribution of integrins and Na+/K+-ATPase to the apical membrane (Mohitorsi et al., 1992; Thadhani et al., 1996; Schrier et al., 2004). Therefore, renal tubular secretion of xenobiotics and endogenous toxins could be also affected by AKI, as this important secretory process is performed by several transporting systems localized in the renal tubular cells. In patients with renal diseases, it was reported that the plasma elimination and renal clearance of the H2 receptor antagonist famotidine were decreased compared with those in healthy volunteers (Manlucu et al., 2005). Famotidine is eliminated mainly by the kidney as the intact form by tubular secretion in addition to glomerular filtration (Lin, 1991). Famotidine was reported to be transported by the rat and human OAT family members rOAT3 and hOAT3, and the OCT family members rOCT1, rOCT2, and hOCT2 (Tahara et al., 2005). Taking these findings into consideration, we hypothesized that decreased renal excretion of famotidine in patients with renal diseases could be caused by the decreased expression and function of OAT and/or OCT family members in the kidney. We reported that renal organic anion transport activity at the basolateral membranes was suppressed in rats with I/R-induced AKI, which was accompanied by down-regulation of both rOAT1 and rOAT3 (Matsuzaki et al., 2007). In contrast, there is little information concerning the regulation of renal OCT family members in AKI. Previously, it was reported that the transport activity of organic cations in renal brush-border membranes was decreased in I/R rats (Maeda et al., 1996). However, there is no information regarding the expression of luminal rMATE1 in association with AKI. In the present study, we examined the pharmacokinetics of cationic drugs and the expression levels of tubular organic cation transporters in I/R-induced AKI rats.

Materials and Methods

Materials. [1-14C]Tetraethylammonium bromide (118.4 MBq/mmol) and d-1-[1-14C]mannitol (525.4 GBq/mmol) were obtained from PerkinElmer Life and Analytical Sciences (Boston, MA). The radiochemical purity of these products was greater than 97% as guaranteed by the company. Famotidine was obtained from Wako Pure Chemicals (Osaka, Japan). All other chemicals used were of the highest purity available.

Experimental Animals. Male Sprague-Dawley rats, initially weighing 200 to 210 g (Cleaa Japan, Inc., Tokyo, Japan), were housed in a standard animal maintenance facility at constant temperature (21–23°C) and humidity (50–70%) with a 12-h light/dark cycle for at least 1 week before the day of the experiment. Our protocol of animal experiments was approved by the committee of the Kumamoto University Institute of Research Development and Analysis. Rats were anesthetized using sodium pentobarbital (50 mg/kg i.p.) and placed on a heating plate (39°C) to maintain a constant temperature. The kidneys were exposed via midline abdominal incisions. Renal ischemia was induced using vascular clamps (A.S. One Company Ltd., Osaka, Japan) over both pedicles for 30 min. After the clamps were released, the incision was closed in two layers with 3-0 sutures. Sham-operated animals underwent anesthesia, laparotomy, and renal pedicle dissection only. All animals received warm saline solution instilled in the peritoneal cavity during the surgical procedure and were then allowed to recover with ad libitum access to food and water. All experiments were performed under surgical anesthesia at 48 h after I/R. Twenty-two of 27 rats survived 48 h after surgery. Blood samples were collected for measurement of blood urea nitrogen (BUN) and serum creatinine (Scr). BUN and Scr in serum were measured at the SRL laboratory (Tokyo, Japan).

Measurement of Plasma Concentration of Famotidine. At 48 h after I/R, famotidine was administered i.v. to rats at 20 mg/kg via the left jugular vein for 1 min. Blood samples (0.4 ml) were collected from the right jugular vein at 5, 15, 30, 60, 120, and 240 min after the injection, and plasma samples were obtained by centrifugation. Urine was also collected for 240 min after injection for determining urinary recovery. The concentration of famotidine in plasma and urine was measured by high-performance liquid chromatography (HPLC). A 100-μl sample of plasma or urine was deproteinized by adding 0.2 ml of methanol and 0.1 ml of the mobile phase and centrifuged at 6000 g for 10 min; 10 μl of the supernatant was injected into HPLC. The HPLC system consisted of an LC-10A DPVP pump (Shimadzu, Kyoto, Japan), an SPD-10AVP ultraviolet spectrophotometric detector (Shimadzu), and a column of TSK-gel ODS 80TM (4.6 mm i.d., 150 mm length; Tosoh, Tokyo, Japan). The mobile phase consisted of a mixture of 30 mM phosphate buffer (pH 7.0) and acetoni-trile (95:5, v/v), and the flow rate was 1.0 ml/min at a column temperature of 40°C. Ultraviolet absorbance was determined at a wavelength of 280 nm. Standard curves for famotidine were prepared over a range of 0.25 to 100 μg/ml and shown to be linear. The coefficients of variation for the desired concentration were 25, and 100 μg/ml ranged from 1.4 to 3.9%. The limit of quantification was 0.25 μg/ml. Blank plasma and urine samples showed no interference with the peak corresponding to famotidine.

Measurement of Plasma and Kidney Concentrations of TEA. At 48 h after I/R, [14C]TEA was administered i.v. to rats at 1.0 mg/kg via the left jugular vein for 1 min. Blood samples (0.4 ml) were collected from the right jugular vein at 5, 15, 30, 60, 120, and 240 min after the injection, and plasma samples were obtained by centrifugation. Urine was also collected for 240 min after injection for determining urinary recovery. At 240 min after injection, kidneys were collected immediately after rats were sacrificed. The excised kidneys were gently washed and weighed. Then 100-μl homogenates of plasma, urine, or kidney were solubilized in 0.5 ml of NCSII (GE Healthcare Bio-Sciences, Piscataway, NJ), and the radioactivity was determined in a liquid scintillation counter after addition of 5 ml of OCS (GE Healthcare Bio-Sciences).

Pharmacokinetic Analysis. A conventional two-compartment model was used to analyze the plasma concentration-time profiles of famotidine and TEA after i.v. administration in rats. The areas under the plasma concentration-time curves (AUCs) for famotidine and TEA were determined by the trapezoidal rule with extrapolation to infinity. Pharmacokinetic parameters calculated using non-linear least squares formula were central volume of distribution (Vc), volume of distribution at steady state (Vss), plasma elimination rate constant (k1), α-phase half-life (t1/2α), β-phase half-life (t1/2β), total body clearance (Clint), and renal clearance (Clren).

Uptake by Rat Renal Slices. Uptake studies in isolated rat renal slices were performed as described in a previous report (Matsuzaki et al., 2007). Briefly, 12 to 15 slices prepared from the whole kidney of sham-operated and ischemic rats (n = 3) were stored in ice-cold oxygenated incubation buffer composed of 120 mM NaCl, 16.2 mM KC1, 1 mM CaCl2, 1.2 mM MgSO4, and 10 mM NaH2PO4/NaHPO4 (pH 7.5). Renal slices were randomly selected and incubated in flasks containing 6 ml of the incubation buffer with [14C]TEA (5 μM, 0.56 kBq/ml). The uptake of these compounds was measured at 37°C under an atmosphere of 100% oxygen. [3H]Mannitol (5 μM, 1.85 kBq/ml) was used to calculate the extracellular trapping and nonspecific uptake of [14C]TEA as well as to evaluate the viability of slices. After incubation for a specified period, the incubation buffer containing radiolabeled compounds was rapidly removed from the flask, and the renal slices were washed twice with 5 ml of ice-cold phosphate-buffered saline, blotted on filter paper, weighed, and solubilized in 0.5 ml of NCSII. The amount of radioactivity was then determined in a liquid scintillation counter after addition of 5 ml of OCS.

Western Blot Analysis. Kidneys (n = 3) were homogenized in homogenization buffer consisting of 230 mM sucrose, 5 mM Tris-HCl (pH 7.5), 2 mM
EDTA, 0.1 mM phenylmethylsulfonyl fluoride, 1 mg/ml leupeptin, and 1 mg/ml pepstatin A. After measurement of the protein content using bicinchoninic acid protein assay reagent (Pierce Chemical, Rockford, IL), each sample (40 μg) was mixed in loading buffer (2% SDS, 125 mM Tris-HCl, 20% glycerol, and 5% 2-mercaptoethanol) and heated at 100°C for 2 min. The samples were separated by 7.5% SDS-polyacrylamide gel electrophoresis and transferred onto polyvinylidene difluoride membranes (Immobilon-P; Millipore Corporation, Bedford, MA) by semidry electroblotting. The blots were incubated with the secondary antibody [horseradish peroxidase-linked mouse immunoglobulin F(ab)2; GE Healthcare Bio-Sciences] for 3 h at room temperature. The blots were washed with TBS-T and incubated with the secondary antibody [horseradish peroxidase-linked anti-rabbit immunoglobulin (f(ab)2); GE Healthcare Bio-Sciences] for 1 h at room temperature. Immunoblots were visualized with an ECL system (ECL Advance Western Blotting Detection Kit; GE Healthcare Bio-Sciences). The relative amount of each band was determined densitometrically using Densitograph Imaging Software (ATTO Corporation, Tokyo, Japan). Densitometric ratios relative to sham-operated rats were used as the reference and accorded an arbitrary value of 100.

**Results**

**Renal Functional Data for I/R-Induced AKI Rats.** Renal function was first examined in rats with renal I/R. As summarized in Table 1, the body weights were slightly yet significantly decreased in I/R rats. The levels of both BUN and SCr were significantly elevated in I/R rats compared with sham-operated rats, indicating that AKI was evoked by I/R treatment.

**Effects of I/R-Induced AKI on Famotidine Pharmacokinetics.** To examine whether the renal disposition of famotidine is decreased in I/R rats in comparison with that in sham-operated rats, we assessed the pharmacokinetics of famotidine. The plasma concentration-time profile of famotidine up to 240 min after i.v. administration is shown in Fig. 1. The plasma concentration of famotidine in I/R rats was higher than that in sham-operated rats. Table 2 summarizes the pharmacokinetic parameters of famotidine in sham-operated and I/R rats. The AUC for famotidine in I/R rats was 2-fold higher than that in sham-operated rats. The Cl_{ren} and Cl_{rat} values for famotidine in I/R rats were significantly decreased to 49 and 14%, respectively, of the corresponding values in sham-operated rats. The $t_{1/2p}$ of famotidine was significantly prolonged in I/R rats compared with that in sham-operated rats, whereas there were no significant differences in the $t_{1/2m}$ of famotidine between the sham-operated and I/R rats.

**Effects of I/R-Induced AKI on TEA Pharmacokinetics.** We next examined the pharmacokinetics of TEA, a typical cationic substrate for rOCT1 and rOCT2. The plasma concentration-time profile of TEA up to 240 min after i.v. administration is depicted in Fig. 2A, and the pharmacokinetic parameters of TEA are summarized in Table 3. I/R caused significant changes in the pharmacokinetic behavior of TEA. The AUC for TEA was markedly elevated in I/R rats compared with that in sham-operated rats. The $K_p$ value in I/R rat kidneys was almost 4-fold higher than that in sham-operated rats. The $V_{ss}$ and $V_{area}$ values in I/R rats were significantly lower in the I/R rats at each time point. The accumulation of TEA in renal slices prepared from sham-operated and I/R rat kidneys. As illustrated in Fig. 3, the accumulation of TEA was significantly lower in the I/R rat kidneys at each time point. The accumulation
of TEA into renal slices at 60 min was significantly decreased to 36% of those in sham-operated rats.

**Protein and mRNA Expression of rOCTs in I/R-Induced AKI Rats.** To get precise information about the decreases in accumulation of TEA in renal slices of I/R rat kidney, we measured renal rOCT1 and rOCT2 expression using Western blot analyses. As is evident in Fig. 4, rOCT2 protein expression was markedly suppressed in I/R rat kidney compared with that in sham-operated rat kidney, whereas there was no significant difference in the expression of rOCT1. The expressions of rOAT1 and rOAT3 protein were significantly depressed in I/R rat kidney, consistent with our previous report (Matsuzaki et al., 2007).

Next, we examined mRNA expression levels of organic cation transporters, rOCT1 and rOCT2, in the kidney (Fig. 4). Compared with sham-operated rat kidneys, the levels of rOCT1 and rOCT2 mRNA in I/R rat kidneys were significantly depressed to 48 and 4%, respectively.

**Protein and mRNA Expression of rMATE1 in I/R-Induced AKI Rats.** The effect of I/R-induced AKI on mRNA and protein expression of rMATE1 was examined. The rMATE1 protein level was markedly depressed in I/R rat kidneys (Fig. 5). As observed for the corresponding protein expression, the relative mRNA expression level of rMATE1 was significantly decreased in I/R rats (Fig. 5).

**Discussion**

Functional changes in renal organic ion transporters may be of clinical relevance, particularly to the use of drugs with high toxicity or a narrow therapeutic range. Serious kidney diseases, such as AKI, influence renal disposition of diverse organic ions in association with decreased glomerular filtration and function of transport systems. Our previous study demonstrated that the mRNA and protein expression levels of organic anion transporters, rOAT1 and rOAT3, were markedly suppressed with I/R-induced AKI, which was accompanied by significant elevation of the serum level of indoxyl sulfate, a uremic toxin that is a substrate of both rOAT1 and rOAT3 (Matsuzaki et al., 2007). In this study, we investigated the change in renal organic cation transporters, rOCT1, rOCT2, and rMATE1.

Three isoforms of organic cation transporter family members, OCT1, OCT2, and OCT3, were identified, and their physiological and pharmacokinetic roles have been evaluated (Inui et al., 2000; Jonker and Schinkel, 2004). rOCT1 is expressed abundantly in the liver and kidney (Gründemann et al., 1994), whereas rOCT2 is expressed predominantly in the kidney but not in the liver (Okuda et al., 1996). These transporters are localized to the basolateral membranes of renal proximal tubules. rOCT3 is expressed predominantly in the placenta but also has been detected in the intestine, heart, brain, lung, and very weakly in the kidney (Kekuda et al., 1998). In the renal proximal tubules of rats, rOCT1 and rOCT2 are considered to mediate the basolateral uptake of various cationic compounds. Previous reports suggested that the pharmacokinetics of famotidine are related to renal function (Manlucu et al., 2005). We found that the renal excretion of famotidine was significantly decreased in I/R rats (Fig. 1; Table 2). A transport study demonstrated that famotidine was a substrate for rOCT1, rOCT2, and rOAT3 (Tahara et al., 2005). Basolateral OCTs are known to be driven by the K⁺ gradient associated with the inside-negative electrical potential difference, generated by Na⁺/K⁺-ATPase (Wright and Dantzler, 2004). We reported that...
Sham I/R excretion of famotidine in I/R may be evoked mainly by the decreased plasma concentration of famotidine in AKI rats, the decreased renal considering the transporter affinity, decreased expression levels, and decreased density to rOAT3, rOCT1, and rOCT2 density to β-actin density in sham-operated (□) and I/R (■) rats. The values for sham-operated rats were arbitrarily defined as 100%. Each column represents the mean ± S.D. from three rats. C, mRNA expressions of basolateral organic ion transporters in the kidney of sham-operated and I/R rats. The values for sham-operated rats were arbitrarily defined as 100%. Each column represents the mean ± S.D. from seven to eight rats. *** p < 0.001 versus sham-operated rats.

Na+/K+−ATPase expression was markedly depressed in the I/R rat kidney (Matsuzaki et al., 2007); thus, the driving force for OCTs at the basolateral membrane could be decreased in I/R rats. As shown in Figs. 2C and 3, organic cation transport activity at the basolateral membranes was reduced in I/R rat kidney, as the Kp value of TEA after i.v. administration and the accumulation of TEA into renal slices were significantly decreased to 20 and 36% of those in sham-operated rats, respectively. We reported previously that the transport activity of rOAT3 in I/R rats was significantly reduced to 52% of that in sham-operated rats, because the accumulation of estrone sulfate, a substrate of rOAT3, was decreased in renal slices from I/R rat kidney (Matsuzaki et al., 2007). It was reported that the Michaelis-Menten constant (Km) values of famotidine for rOCT1, rOCT2, and rOAT3 were 87, 61, and 345 μM, respectively (Tahara et al., 2005). In addition, the mRNA expression of not only rOCT2 but also rOCT1 was significantly suppressed in I/R rat kidneys (Fig. 4). The decrease in rOCT2 mRNA was remarkable compared with that in rOCT1 mRNA, suggesting that rOCT2 was more sensitive to I/R-induced AKI. Recently, it was reported that the expression of rOCT2 was decreased in rats with chronic renal failure (Ji et al., 2002), hyperuricemia (Habu et al., 2003), and diabetes mellitus (Thomas et al., 2004). Urakami et al. (2000) reported that the expression of rOCT2 was up-regulated by testosterone and down-regulated by estradiol in rats. It was also suggested that the lowered plasma level of testosterone was responsible for the decreased rOCT2 expression (Ji et al., 2002). Testosterone induces the expression of rOCT2 but not that of rOCT1 and rOCT3 via the androgen receptor-mediated transcriptional pathway (Asaka et al., 2006). However, it has been reported that there were no significant changes in plasma testosterone and estradiol after renal I/R-induced AKI (Park et al., 2004), although serum testosterone levels were decreased in bilateral ureteral ligation and uranyl nitrate or cisplatin-induced AKI (Ivic et al., 1988; Masubuchi et al., 2006). Therefore, further study on the factor(s) and mechanisms of the
decreased expression of rOCT2 is required to understand its regulation in AKI states. In vivo renal clearances of fotamidine and TEA were significantly decreased in I/R rats. Renal clearance of fotamidine and TEA may be affected by organic cation transport activity not only at the basolateral membranes but also at the brush-border membranes, as renal secretion is performed by two transport steps in both membranes. In the rat renal tubular brush-border membranes, rMATE1 can mediate the organic cation transport energized by an inward-directed H⁺ gradient, which is mainly generated by Na⁺/H⁺ exchanger (NHE) 3 (Moe, 1999). In five-sixths nephrectomized rats, the down-regulated expression of luminal rMATE1 was correlated well with the tubular secretion of cimetidine, and the expression of NHE3 was markedly depressed (Nishihara et al., 2007). TEA and cimetidine are substrates for rMATE1 (Ohta et al., 2006; Terada et al., 2006), although the ability of rMATE1 to recognize fotamidine as a substrate is as yet unknown. We found that the protein and mRNA expressions of rMATE1 were markedly depressed in I/R rats (Fig. 5). Previously, it was reported that NHE3 expression was markedly depressed in I/R rats (Wang et al., 1997; Kwon et al., 2000), and the transport activity of organic cations in renal brush-border membranes was decreased in I/R rats (Maeda et al., 1993). Therefore, down-regulation of rMATE1 could be involved in the decreased renal clearance of TEA in I/R rats at the luminal membranes.

We have reported that I/R-induced AKI caused the down-regulation of basolateral rOCT2, accompanied by decreased organic cation transport activities at the basolateral membrane. Furthermore, luminal rMATE1 expression was markedly depressed in I/R rats, suggesting decreased organic cation transport activities at brush-border membranes. The present results suggest that the renal expressions of rOCT2 and rMATE1 are down-regulated and the urinary secretion of caticnic drugs is decreased in AKI. Our findings provide information for understanding the mechanisms involved in pharmacokinetic alteration of drugs excreted mainly into urine under AKI, and the physiopathological roles of basolateral rOCTs and luminal rMATE1.

References


Matsuzaki ET al. doi:10.1093/mdr/mdw001


Address correspondence to: Dr. Hideyuki Saito, Department of Pharmacy, Kumamoto University Hospital, 1-1-1 Honjo, Kumamoto 860-8556, Japan. E-mail: saitohide@kcf.kuh.kumamoto-u.ac.jp.