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Different transport properties between famotidine and cimetidine by human renal organic ion transporters (SLC22A)

Hideyuki Motohashi, Yuichi Uwai, Kiyo Hiramoto, Masahiro Okuda, Ken-ichi Inui*

Department of Pharmacy, Kyoto University Hospital, Faculty of Medicine, Kyoto University, Sakyo-ku, Kyoto 606-8507, Japan

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Abstract

Histamine H_2 receptor antagonist famotidine and cimetidine are commonly used for treatment of gastrointestinal ulcer diseases. Inasmuch as these drugs are mainly secreted by renal tubules, dosages have been adjusted according to renal function. Although many studies have been performed on the molecular mechanisms of renal handling of cimetidine, little is known about that of famotidine. In this study, to examine the recognition and transport of famotidine by human organic anion transporters (OATs; hOAT1, hOAT3) and human organic cation transporter (OCT; hOCT2), the uptake studies using *Xenopus laevis* oocytes were performed in comparison with cimetidine. The half-maximal inhibitory concentrations of famotidine for [^{3}H]estrone sulfate transport by hOAT3 and [^{14}C]tetraethylammonium transport by hOCT2 (300 μM and 1.8 mM, respectively) were higher than those of cimetidine (53 and 67 μM, respectively). While cimetidine inhibited *p*-[^{14}C]aminohippurate transport by hOAT1 in a concentration dependent manner, famotidine did not affect it at 5 mM. In addition, hOAT3 mediated famotidine uptake, but hOAT1 and hOCT2 did not show famotidine transport. These results indicate that there are marked differences between famotidine and cimetidine in the recognition and transport by organic ion transporters and that hOAT3 contributes to the renal tubular secretion of famotidine. Present findings should be useful information to understand the renal handling of famotidine and cimetidine.

Keywords: Organic anion transporter; Organic cation transporter; Famotidine; Cimetidine; Renal tubular secretion

1. Introduction

A histamine H_2 receptor antagonist famotidine is commonly used in the treatment for gastrointestinal ulcer diseases. Famotidine shows beneficial characteristics, including stronger inhibition of gastric acid secretion, longer acting and less interaction with P-450, compared with another histamine H_2 receptor antagonist cimetidine (Howard et al., 1985; Humphries, 1987). Pharmacokinetic studies revealed that famotidine was mainly excreted into the urine as an unmetabolized form (Takabatake et al., 1985; Lin et al., 1988; Dowling et al., 2001). Renal clearance of famotidine exceeded the creatinine clearance about three times in subjects with normal renal function, indicating the efficient tubular secretion of the drug. In patients with renal insufficiency, plasma elimination and renal clearance of famotidine were significantly decreased (Takabatake et al., 1985; Lin et al., 1988). To avoid the accumulation and undesirable effects, famotidine dosage should be reduced according to the renal functions.

In this decade, organic anion transporters (OATs) and organic cation transporters (OCTs) in the kidney were identified, and their characteristics have been clarified. These transporters mediate endogenous and exogenous substances, such as uremic toxins, diuretics, methotrexate, antibiotics, antivirals and nonsteroidal antiinflammatory drugs, suggesting that OATs and OCTs are responsible for the tubular secretion of these compounds (Inui et al., 2000; Sekine et al., 2000; Dresser et al., 2001). Recently, we quantified mRNA levels of organic ion transporters in the

* Corresponding author. Tel.: +81 75 751 3577; fax: +81 75 751 4207.
E-mail address: inui@kuhp.kyoto-u.ac.jp (K. Inui).

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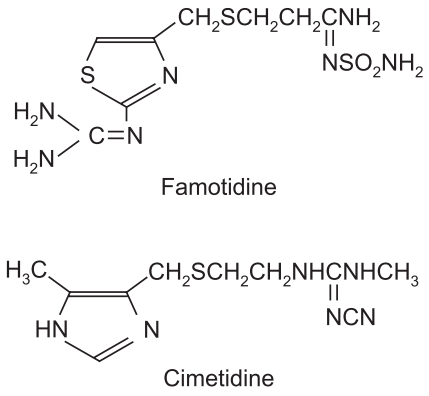

Fig. 1. Chemical structures of famotidine and cimetidine.

human kidney cortex and revealed that hOAT1 (SLC22A6), hOAT3 (SLC22A8) and hOCT2 (SLC22A2) mRNA were higher than other organic ion transporters (Motohashi et al., 2002). Moreover, hOAT1, hOAT3 and hOCT2 protein localized at the basolateral membrane of the renal proximal tubules. Accordingly, these transporters play important roles for the renal uptake of organic compounds from the circulation.

It has been assumed that the renal tubular secretion of famotidine and cimetidine would be mediated by OCTs due to their cationic property at the physiological pH (Fig. 1). Indeed, cimetidine inhibits the renal secretion of various organic cations (Somogyi et al., 1983; Christian et al., 1984; van Crugten et al., 1986) and Urakami et al. (2001, 2002) indicated that rat and human organic cation transporters rOCT1, rOCT2 and hOCT2 transported cimetidine. However, in addition to hOCT2, hOAT1, hOAT3 and rOAT3 were shown to transport the cimetidine. (Kusuhara et al., 1999; Cha et al., 2001; Burckhardt et al., 2003). Therefore, it was supposed that these three transporters were concerned with renal secretion of cimetidine. While famotidine is more frequently used than cimetidine because of it beneficial characteristics, adverse effects associated with famotidine, such as thrombocytopenia (Wade et al., 2002) or central nerve system reaction (Yoshimoto et al., 1994), have been reported. Although dosage should be adjusted according to renal function, molecular mechanisms of renal secretion of famotidine have not been investigated in contrast to cimetidine. To understand the renal handling of famotidine, it should be examined whether hOATs or hOCTs recognize and transport famotidine.

The purpose of the present study is to clarify the recognition and transport properties of famotidine by hOAT1, hOAT3 and hOCT2 in comparison with cimetidine. We performed transport experiments of famotidine and cimetidine using *Xenopus laevis* oocytes expressing these organic ion transporters.

2. Materials and methods

2.1. Materials

p-[Glycyl-^{14}C]aminohippurate (PAH; 1.9 GBq/mmol), [1-^{14}C]tetraethylammonium bromide (TEA; 88.8 MBq/mmol) and [6,7-^{3}H(N)]estrone sulfate were obtained from Perkin-Elmer Life Science Products (Boston, MA, USA). Famotidine and cimetidine were purchased from Wako Pure Chemical Industries (Osaka, Japan) and Nacalai Tesque (Kyoto, Japan), respectively. Unlabeled PAH and estrone 3-sulfate were from Sigma (St. Louis, MO, USA). 1-Methyl-4-phenylpyridinium (MPP) was from Research Biochemicals International (Natick, MA, USA). All other chemicals used were of the highest purity available.

2.2. Transport experiments using X. laevis oocytes expressing hOAT1, hOAT3 and hOCT2

Functional analyses of the organic ion transporters using *X. laevis* oocytes were carried out according to our previous report (Uwai et al., 2000). Briefly, the capped cRNA was transcribed from *Xba*I-linearized pSPORT1 containing hOAT1, hOAT3 or hOCT2 cDNA with T7 RNA polymerase. After the injection of 50 nl of water or the cRNA (25 ng) into oocytes, the oocytes were maintained in modified Barth's medium (88 mM NaCl, 1 mM KCl, 0.33 mM

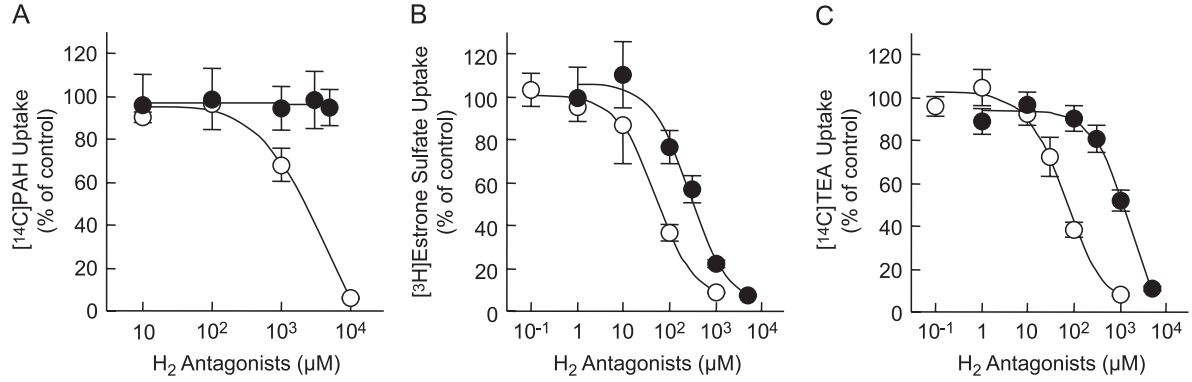

Fig. 2. Inhibitory effects of famotidine and cimetidine on organic ion uptake by hOAT1 (A)-, hOAT3 (B)- and hOCT2 (C)-expressing oocytes. hOAT1-, hOAT3- or hOCT2-expressing oocytes were incubated with 25 μM [^{14}C]PAH, 18.87 nM [^{3}H]estrone sulfate or 36 μM [^{14}C]TEA, respectively, in the absence (control) or presence of famotidine (●) or cimetidine (○) at various concentrations for 1 h. Each point represents the mean±S.E.M. of 7 to 10 oocytes.

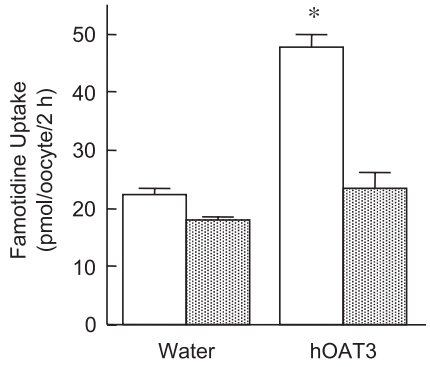

Fig. 3. Uptake of famotidine by hOAT3-expressing oocytes. Water-injected or hOAT3-expressing oocytes were incubated with 1 mM famotidine in the absence (open column) or presence (dotted column) of 1 mM estrone sulfate for 2 h. Each column represents the mean±S.E.M. of five to eight measurements. Four oocytes were used for each uptake measurement. *P<0.05, significantly different from the other three columns.

$Ca(NO_3)_2$, 0.4 mM $CaCl_2$, 0.8 mM $MgSO_4$, 2.4 mM $NaHCO_3$ and 10 mM HEPES; pH7.4) with 50 μg/ml of gentamicin at 18 °C for 3 days. The uptake reaction of [^{14}C]PAH, [^{3}H]estrone sulfate or [^{14}C]TEA was initiated in a 24-well plate by incubating the oocytes in 500 μl of uptake buffer (96 mM NaCl, 2 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$ and 5 mM HEPES; pH7.4) in the absence or presence of each histamine H_2 receptor antagonist for 1 h at 25 °C. After washing the oocytes with 2 ml of ice-cold uptake buffer five times, each oocyte was transferred to a scintillation vial and dissolved in 300 μl of 10% sodium lauryl sulfate. The inhibitory effects of famotidine and cimetidine were evaluated by measuring the radioactivity of each solubilized oocyte in 3 ml of Aqueous Counting Scintillant (ACS) II (Amersham International, Buckinghamshire, UK). Uptake experiments of famotidine and cimetidine were performed by incubating oocytes in 100 μl of the uptake buffer with or without each transporter's specific inhibitor for 2 h at 25 °C in a 1.5-ml tube. After the incubation, the oocytes were washed with 1.5 ml of ice-cold uptake buffer three times. Two hundred microliters of extraction solution (30 mM phosphate buffer [pH7.0] in methanol at 1:1) was added into the tubes and sonicated. The homogenate was centrifuged at 14,000 rpm for 20 min, and the supernatant was filtrated through a Millipore filter (SJGVL; 0.45 μM). Famotidine and cimetidine taken up by oocytes were determined by high-performance liquid chromatography.

2.3. Quantification of famotidine and cimetidine by high-performance liquid chromatography

High-performance liquid chromatograph LC-10AS (Shimadzu, Kyoto, Japan) equipped with a UV spectrophotometric detector (SPD-10AV; Shimadzu) and an integrator (Chromatopac C-R1A; Shimadzu) was used for the measurement of famotidine and cimetidine under the following conditions: column, TSK-gel ODS 80TM with 4.6-mm inside diameter and 150-mm length (Tosoh, Tokyo, Japan); mobile phase, 30 mM phosphate buffer (pH7.0) in methanol at 82:18 for famotidine and 70:30 for cimetidine; flow rate, 0.8 ml/min; wavelength, 266 nm for famotidine and 235 nm for cimetidine; and temperature, 40 °C. The detection limit was 0.2 μM for famotidine and 0.1 μM for cimetidine.

2.4. Statistical analysis

Statistical analysis was performed by the one-way analysis of variance followed by Scheffe's test.

3. Results

3.1. Inhibitory effects of famotidine and cimetidine on hOAT1, hOAT3 and hOCT2

To assess whether famotidine interacts with hOAT1, hOAT3 and hOCT2, we examined its inhibitory effects on organic ion transporters (Fig. 2). Famotidine at 5 mM completely inhibited [^{3}H]estrone sulfate transport by hOAT3 and [^{14}C]TEA transport by hOCT2 but did not affect [^{14}C]PAH uptake by hOAT1. To compare the inhibitory potencies of famotidine for the transport activity

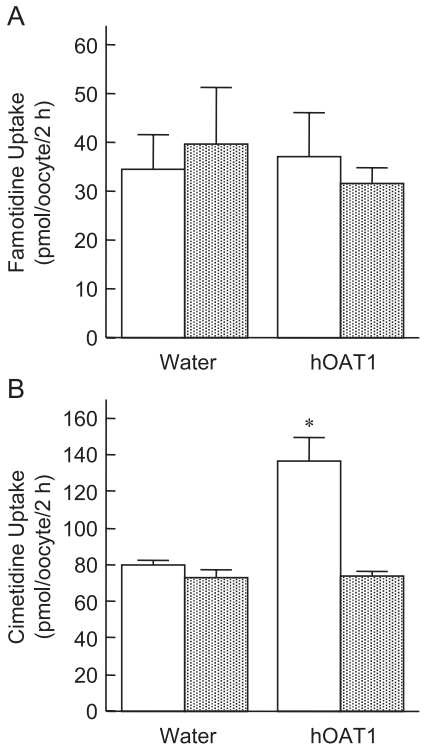

Fig. 4. Uptake of famotidine (A) and cimetidine (B) by hOAT1-expressing oocytes. Water-injected or hOAT1-expressing oocytes were incubated with famotidine or cimetidine at 2 mM in the absence (open column) or presence (dotted column) of 1 mM PAH for 2 h. Each column represents the mean±S.E.M. of five to eight measurements. Four oocytes were used for each uptake measurement. *P<0.05, significantly different from the other three columns.

of hOAT3 and hOCT2 with those of cimetidine, half-maximal inhibitory concentrations (IC_{50}) were estimated. As shown in Fig. 2B and C, the apparent IC_{50} values of famotidine were estimated to be 300 μM for hOAT3 and 1.8 mM for hOCT2. On the other hand, the apparent IC_{50} values of cimetidine were 53 and 67 μM for hOAT3 and hOCT2, respectively (Fig. 2B and C). In contrast to famotidine, cimetidine inhibited the transport of [^{14}C]PAH by hOAT1 in a concentration-dependent manner (Fig. 2A). The estimated IC_{50} values of famotidine for these three transporters were higher than those of cimetidine.

3.2. Transport of famotidine and cimetidine by hOAT1, hOAT3 and hOCT2

Famotidine transport by hOAT1, hOAT3 or hOCT2 was examined using Xenopus oocyte expression system. As shown in Fig. 3, famotidine uptake into the hOAT3-expressing oocytes significantly exceeded that into water-injected oocytes. Estrone sulfate completely inhibited the famotidine uptake to the level of water-injected oocytes. These findings indicate that famotidine is a substrate for hOAT3. In contrast to hOAT3, famotidine uptake values by hOAT1- and hOCT2-expressing oocytes were not different from those by water-injected oocytes (Figs. 4A and 5A). In addition, we evaluated the cimetidine uptake by hOAT1 and hOCT2 to compare with famotidine. As shown in Figs. 4B and 5B, injection of hOAT1 and hOCT2 cRNA in oocytes stimulated the cimetidine uptake. PAH or MPP reduced the cimetidine accumulation in hOAT1- or hOCT2-expressing oocytes to those of water-injected control, respectively.

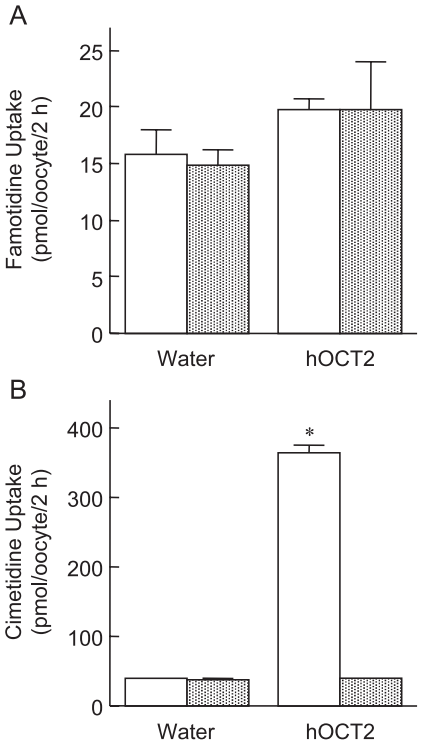

Fig. 5. Uptake of famotidine (A) and cimetidine (B) by hOCT2-expressing oocytes. Water-injected or hOCT2-expressing oocytes were incubated with famotidine or cimetidine at 1 mM in the absence (open column) or presence (dotted column) of 5 mM MPP for 2 h. Each column represents the mean±S.E.M. of five to eight measurements. Four oocytes were used for each uptake measurement. *P<0.05, significantly different from the other three columns.

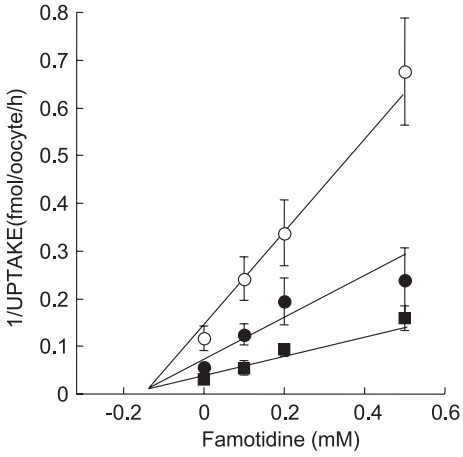

Fig. 6. Dixon plot for inhibitory effects of famotidine on [^{3}H]estrone sulfate uptake by hOAT3-expressing oocytes. hOAT3-expressing oocytes were incubated with [^{3}H]estrone sulfate (20 nM, ○; 40 nM, ●; 80 nM, ■) with famotidine at the indicated concentrations for 1 h. The levels of [^{3}H]estrone sulfate uptake was determined, and figures were drawn after subtraction of the uptake in water-injected oocytes from that in hOAT3 cRNA-injected oocytes. Values are represented as 1/uptake. Each point represents the mean±S.E.M. of 7 to 10 oocytes.

We performed Dixon plot analysis to determine the inhibitory mode of famotidine on the hOAT3 mediated estrone sulfate uptake, and the results were shown in Fig. 6. Famotidne inhibited competitively, and apparent Ki value was estimated to be 179±24 μM.

4. Discussion

In this study, we examined whether basolateral organic ion transporters such as hOAT1, hOAT3 and hOCT2 recognized famotidine as substrate in comparison with cimetidine. It was shown that there were marked differences between famotidine and cimetidine in the recognition and transport properties by renal organic ion transporters.

It was indicated that efficient tubular secretion contributed to renal excretion of famotidine and cimetidine in subjects with normal renal function. Inasmuch as these drugs are weak bases, it has been speculated that renal secretion of famotidine and cimetidine are mediated by the organic cation transporter. In the case of cimetidine, Urakami et al. (2001, 2002) demonstrated that the cimetidine was transported by rOCT2 and hOCT2, and similar results were obtained in this study (Fig. 5B). Furthermore, in 5/6 nephrectomized rats, renal clearance of cimetidine showed a significant correlation with rOCT2 expression levels in the kidney (Ji et al., 2002). Therefore, hOCT2 may contribute to the renal secretion of cimeti-

dine. Unexpectedly, hOCT2 did not show any famotidine transport (Fig. 5A). Due to the detection limit of HPLC analysis, the uptake experiments were performed at 1 mM. It is possible that saturation of the transporter make it difficult to detect the transport of famotidine by hOCT2. However, as expected and as opposed to famotidine, cimetidine transport by hOCT2 was detected. Arndt et al. (2001) reported that some organic cations, such as quinine and tetrapentylammonium, inhibited rOCT2 but that these compounds seemed to be not translocated via rOCT2. Therefore, it is likely that famotidine inhibits hOCT2 but is hardly transported by hOCT2 differently from cimetidine. Recently, Lee et al. (2002) reported that famotidine was not transported by the TEA-sensitive organic cation transport systems across the basolateral membrane in LLC-PK_1 cells. Inasmuch as LLC-PK_1 cells retain basolateral organic cation transporter of the kidney (Saito et al., 1992), the report of Lee et al. (2002) is consistent with our results. These data suggest that hOCT2 is involved in the basolateral transport of cimetidine but not of famotidine in the human kidney.

Recently, cimetidine was reported to be a substrate for hOAT1 and hOAT3 in addition to hOCT2 (Cha et al., 2001; Burckhardt et al., 2003), and our present results are consistent with these reports. Gisclon et al. (1989) reported that probenecid, a classic inhibitor of organic anion, decreased the renal clearance of cimetidine. It was implied that organic anion transporters were concerned with renal secretion of cimetidine. However, in the report of Gisclon et al. (1989), interaction between cimetidine and probenecid was transient and slight. Although further studies are needed to calculate the contribution of hOATs for cimetidine excretion, it is speculated that organic anion transporters play minor roles for renal secretion of cimetidine. On the other hand, Inotsume et al. (1990) reported that probenecid had a pronounced effect on renal tubular secretion of famotidine. The tubular secretory clearance of famotidine was decreased to one-tenth by coadministration of probenecid. As probenecid is well known as a potent inhibitor for hOAT3, their report is consistent with our present results that hOAT3, but not hOCT2, mediated famotidine uptake. Therefore, it is suggested that hOCT2 plays one of the important roles for renal uptake of cimetidine and hOAT3 for famotidine uptake, respectively.

Dowling et al. (2001) showed that tubular secretion of famotidine in human was not saturated at its unbound plasma concentrations up to about 10 μM. In the present study, the estimated Ki value of famotidine for hOAT3 was 179 μM (Fig. 6), suggesting that the famotidine transport by hOAT3 was not saturated at the therapeutic levels. Boom et al. (1996) reported that the apparent Michaelis–Menten constant (K_T) for tubular secretion of famotidine in vivo was 76 μM using the beagle dog. The K_T value in the report of Boom et al. is lower than the Ki value of famotidine for hOAT3 (179 μM) in this study. At present, it is difficult to discuss the difference between the K_T value of Boom et al. and our Ki value because of various factors such as species difference and experimental conditions.

It is well known that cimetidine reduces the renal secretion of procainamide (Somogyi et al., 1983), although famotidine had no effect on the pharmacokinetics of procainamide (Klotz et al., 1985). In this study, we assessed the inhibitory potency of cimetidine on hOCT2, the candidate responsible for the renal uptake of procainamide. The IC_{50} of the cimetidine for hOCT2 was around its therapeutic plasma concentration. Therefore, cimetidine may block the hOCT2 transport activity in vivo. On the other hand, the inhibitory potency of famotidine for hOCT2 was weaker than that of cimetidine, and the clinical plasma levels of famotidine (0.15 ± 0.06 μM; Yoshimoto et al., 1994) were extremely lower than the IC_{50} for hOCT2. Therefore, famotidine cannot inhibit hOCT2 transport in the kidney at the therapeutic dose. In this study, the IC_{50} of famotidine for hOAT3 was also much higher than the clinical plasma concentration, and famotidine did not interact with hOAT1. Differently from cimetidine, famotidine is not likely to inhibit the tubular secretion of other drugs via these organic ion transporters, hOAT1, hOAT3 and hOCT2.

Several reports represented that pharmacokinetics of famotidine was related with renal function (Takabatake et al., 1985; Lin et al., 1988). Dosage adjustment of famotidine is necessary for the patients with renal insufficiency. In our previous studies, expression levels of renal drug transporters were altered in the impaired kidney. The expression level of rOCT2 was decreased in the 5/6 nephrectomized rats, but those of rOAT1, rOAT3 and rOCT1 were not influenced (Ji et al., 2002). Hyperuricemic rats represented the down-regulation of rOAT1, rOAT3 and rOCT2 but not of rOCT1 (Habu et al., 2003). Recently, we reported the alteration of organic ion transporters in the kidney of renal disease patients (Sakurai et al., 2004). In that report, elimination rate of cefazolin, which is substrate for hOAT3, was correlated with hOAT3 mRNA level, suggesting that the expression levels of renal drug transporter affect urinary drug excretion. It is interesting whether renal excretion of famotidine is affected by hOAT3 expression level in the patients with renal insufficiency.

In conclusion, this study represented the differences between famotidine and cimetidine in the interaction with human renal organic ion transporters, hOAT1, hOAT3 and hOCT2, and suggested that hOAT3 contributed to the renal tubular secretion of famotidine. Theses findings could be useful information to understand the renal handling of famotidine and to make optimum dosage regimens of the histamine H_2 receptor antagonists.

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