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Relative contribution of absorptive and secretory transporters to the intestinal absorption of fexofenadine in rats

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ABSTRACT

It has been shown that fexofenadine, a selective non-sedating histamine H_1-receptor antagonist, is a substrate for P-glycoprotein (P-gp) and an organic anion transporting peptide (OATP). This study was undertaken to investigate the relative contribution of these absorptive and secretory transporters to the intestinal absorption of fexofenadine in rats. When 0.1 mM fexofenadine was introduced into duodenal, jejunal, and ileal loops, its disappearance was around 10% over 30 min. Cyclosporine A, but not ketoconazole, probenecid or mitoxantron, significantly increased fexofenadine disappearance in the ileal loops. The serosal-to-mucosal permeation of fexofenadine across the rat ileal segments was approximately 18-fold greater than its mucosal-to-serosal permeation. The secretory orientation of the ileal permeation of fexofenadine was weakened significantly in the presence of cyclosporine A, moderately in the presence of ketoconazole, but was unchanged in the presence of probenecid. When fexofenadine (0.1 or 0.5 mM) was administered to rats intraluminally, plasma concentrations increased linearly up to 120 min. The magnitude of the increase in plasma fexofenadine concentrations in the presence of cyclosporine A was more remarkable at 0.5 mM than at 0.1 mM. The results obtained in this study suggest that the intestinal absorption of fexofenadine is relatively small in rats even if OATP functions as an absorptive transporter for fexofenadine. Low absorption of fexofenadine in rats is attributed to potent secretory transport mediated by P-gp.

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1. Introduction

Fexofenadine, a selective non-sedating histamine H_1-receptor antagonist, is orally administered in the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria (Simpson and Jarvis, 2000). After ingestion, fexofenadine is minimally metabolized (less than 5% of the dose) and excreted largely unchanged in the urine and feces (about 11 and 80% of the dose, respectively) in humans (Molimard et al., 2004). As the oral bioavailability of fexofenadine is estimated to be at least 33% in humans (Molimard et al., 2004), biliary excretion is considered to be extensive. Using in vitro and animal models, many studies have suggested that fexofenadine is a good substrate for P-glycoprotein (P-gp, *ABCB1*) (Cvetkovic et al., 1999; Perloff et al., 2002; Petri et al., 2004; Tahara et al., 2005). P-gp is highly expressed in normal tissues such as the intestine, liver, kidney, brain, placenta and testis, and plays important roles in the disposition of xenobiotics (Ito et al., 2005). Intestinal P-gp restricts the absorption of its substrates to various extents. It is, therefore, likely that fexofenadine absorption is strongly suppressed by P-gp. Supporting previous in vitro results, it has been demonstrated that itraconazole, a P-gp inhibitor, was capable of significantly increasing plasma concentrations of fexofenadine in humans (Shimizu et al., 2006).

On the other hand, on the behalf of observations that verapamil and ketoconazol, both potent P-gp inhibitors, failed to modulate intestinal transport of fexofenadine in humans, some reports have suggested that intestinal P-gp is much less involved in limiting fexofenadine absorption (Tannergren et al., 2003a,b). At present, no definite hypothesis can be drawn from the inconsistent results of these studies. Another possibility is that secretory transporters other than P-gp are involved in the intestinal absorption of fexofenadine. In addition to P-gp, multidrug-resistance associated protein 2 (MRP2/mrp2, *ABCC2*) and breast cancer resistance protein (BCRP/bcrp, *ABCG2*) are highly expressed on the brush-border membranes of intestinal epithelial cells (Dietrich et al., 2003). However, the involvement of these ABC transporters in the absorption of fexofenadine has not yet been fully addressed.

Moreover, evidence exists to indicate that fexofenadine is a potent substrate for an organic anion transporting polypeptide (OATP), an absorptive transporter (Cvetkovic et al., 1999; Nozawa

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et al., 2004; Kikuchi et al., 2006). Grapefruit juice, orange juice, and apple juice lowered the oral bioavailability of fexofenadine, implying the interference of OATP-mediated fexofenadine absorption by some ingredients in these fruit juices (Dresser et al., 2002). Therefore, increasing attention has been paid to the clinical relevance of OATP-mediated fexofenadine absorption in vivo. Very recently, Bailey et al. (2007) reported that naringin, an ingredient in grapefruit juice, is a selective inhibitor of OATP1A2-mediated fexofenadine transport.

Although the transport of fexofenadine by P-gp and OATP was studied under in vitro conditions, the relative contribution of these transporters to fexofenadine absorption has not well characterized in situ or in vivo. Modulation of absorptive and secretory transporters often triggers clinically relevant drug–drug interactions. It is, therefore, important to know the magnitudes of the relative contributions of these transporters to the overall intestinal absorption of fexofenadine. In this study, by focusing on the changes in the intestinal transport of fexofenadine in the presence of various modulators of secretory transporters, we addressed the relative contribution of secretory transporters in rats.

2. Materials and methods

2.1. Materials

Fexofenadine hydrochloride was purchased from Toronto Research Chemicals Inc. (North York, Ontario, Canada). Cyclosporine A, ketoconazole, *p*-aminohippuric acid (PAH) and benzylpenicillin potassium were purchased from Wako Pure Chem. Ind. (Osaka, Japan). Probenecid and mitoxantron dihydrochloride were purchased from Sigma–Aldrich (St. Louis, MO, USA). Other reagents were of the highest grade available.

2.2. In situ absorption experiments using loop technique

In the present study, principles of good laboratory animal care were followed and animal experimentation was performed in compliance with the Guidelines for the Care and Use of Laboratory Animals in Health Sciences University of Hokkaido.

Tyrode's solution (137 mM NaCl, 3 mM KCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, 12 mM $NaHCO_3$, 0.4 mM NaH_2PO_4) including 6 mM D-glucose was used as an experimental medium. After fasting for 15–18 h, male Wistar rats (Hokudo, Sapporo, Japan) weighing 300–370 g were anesthetized by the intraperitoneal administration of sodium pentobarbital (40 mg/kg), and three loops (each 10 cm in length) were prepared in the duodenal, jejunal and ileal regions in each rat, as described previously (Saitoh et al., 1998). The proximal ligature of the duodenal loop was placed approximately 1 cm from the pylorus, that of the jejunal loop was placed approximately 10 cm from the terminal ligature of the duodenal loop, and that of the ileal loop was placed about 15 cm above the ileocecal junction. The bile duct was tied in all experiments to prevent the influx of bile into the lumen. After the contents of each loop were gently flushed out with approximately 10 ml of saline, both ends of each loop were tied and 1 ml of drug solution was injected into the loops with a syringe. The entire intestine was then restored to the abdominal cavity and body temperature was maintained during anesthesia by heating the rat with a lamp. Saline and test solutions were warmed to approximately 37 °C in advance. The pH of the drug solution was fixed at 6.5 in all absorption experiments. At 30 min after injection of the drug solution, all loops were quickly isolated from the body and the rat was sacrificed. The blood adhering to the outer surface of each loop was washed away with ice-cold saline and the contents of each loop were then emptied into a 10-ml volumetric flask. The inner side of each loop was rinsed with saline to give a final volume of 10 ml. An aliquot (0.1 ml) of the well-stirred sample was vigorously mixed with an equal volume of methanol and let stand for 10 min in iced water. The mixture was then centrifuged at 5500 × *g* for 10 min at 5 °C and the supernatant was applied to assay drug concentrations. The results obtained from this treatment were taken as the drug remaining in loop fluid. To determine the drugs adhering to or accumulated in the mucosa, the mucosa of each loop was gently scraped using a slide glass and homogenized in 4 ml of Tyrode's solution (pH 6.5) using a polytron (Kinematica, Lucerne, Switzerland). An aliquot (0.1 ml) of the homogenate was taken and mixed with an equal volume of methanol and then let stand for 10 min in iced water. The mixture was then centrifuged at 5500 × *g* for 10 min at 5 °C and the supernatant was applied to assay drug concentrations.

In some experiments, the plasma concentrations of fexofenadine were determined after administration as a solution into an entire small intestinal loop (approximately 60 cm), which was prepared by placing the upper ligature 10 cm from the pylorus and the lower ligature 10 cm above the ileocecal junction. After washing out the loop contents with approximately 50 ml of saline, 6 ml of fexofenadine solution (pH 6.5) was introduced into the loop from the upper side with a syringe. Just before administration and at 10, 30, 60, 90 and 120 min after administration, 0.5 ml of blood was collected from the jugular vein under anesthesia for the assay of fexofenadine concentrations. After the final blood collection, the loop was quickly isolated from the body and the rat was sacrificed. The blood adhering to the outer surface of the loop was washed away with ice-cold saline and the loop contents were then emptied into a 100-ml volumetric flask. The inner side of the loop was rinsed with saline to give a final volume of 100 ml. The loop sample was handled as described above. The area under the plasma concentration–time curve (AUC) was calculated using the trapezoidal method.

2.3. In vitro permeation experiments using rat ileal segments

In vitro permeation experiments across rat ileal segments were performed using diffusion cells (Corning Costar, Acton, MA, USA) as described previously (Saitoh et al., 1997). The surface area available for permeation was 1.78 cm^2. The pH of the Tyrode's solution and drug solution was fixed at 7.4 in all permeation experiments. After overnight fasting, male Wister rats weighing 330–450 g were anesthetized with ether and the entire small intestine was quickly removed and rinsed in ice-cold saline. The 10-cm section immediately distal to the pylorus was discarded. The contents of the remaining section were flushed out with ice-cold saline and then the section was cut in two. The lower part of small intestine was kept as the ileal portion in ice-cold saline. Ileal segments (approximately 4 cm in length) were cut off and placed in ice-cold Tyrode's solution, which had been fully gassed with 95%O_2–5%CO_2, until use. Each segment was cut longitudinally and mounted onto the pins of the diffusion cells, and the cell halves were clamped together. To the donor compartment was added 7 ml of drug solution, and to the receiving compartment was added drug-free Tyrode's solution. Both solutions had been pre-warmed to 37 °C. The diffusion cells were fixed on exclusive heating blocks and their temperature were maintained at around 37 °C during the experiment. The fluids in both compartments were circulated by gas lift with 95% O_2–5% CO_2 and 0.5 ml of receiver solution was taken at the designated time points until 120 min for the measurement of fexofenadine, which permeated in both the mucosal-to-serosal (M-to-S, absorptive) and serosal-to-mucosal (S-to-M, secretory) directions. Drug-free Tyrode's solution (0.5 ml) was added to the receiver compartment after each sampling. The cumulative amount was plotted *vs.* time

for each permeation experiment. Permeation rate was calculated from the slope of the linear portion of the amount permeating *vs.* time plot. The tissue mounting process was completed within 30 min after resection of the small intestine.

2.4. Analyses

Fexofenadine was assayed using a Shimadzu LC-6A or LC-10A HPLC system (Shimadzu, Kyoto, Japan) equipped with a Shimadzu RF-10A$_{XL}$ fluorescence detector or SPD-10AV$_{VP}$ UV–vis detector. The column used was Inertsil ODS-3 (4.6 mm × 250 mm, 5 μm, Nakarai Tesque, Kyoto, Japan). The other chromatographic conditions for fexofenadine were as follows: mobile phase, 0.05 M KH_2PO_4–CH_3CN (55:45 for loop fluids and permeation samples, 65:35 for plasma samples); wavelength, excitation 230 nm, emission 280 nm; column temperature, 50 °C; flow rate, 0.8 ml/min; and injection volume, 20–50 μl.

2.5. Statistical analysis

Data are expressed as the mean with S.E. obtained from at least three rats. Statistical analysis was performed using Student's *t*-test and $p < 0.05$ was considered significant.

3. Results

3.1. Disappearance of fexofenadine from rat intestinal loops

When fexofenadine was administered alone into the intestinal loops at a concentration of 0.1 mM, percentage disappearance over 30 min was relatively low with only 14, 7 and 4% of the dose from the duodenum, jejunum and ileum, respectively (Table 1). The amount of fexofenadine recovered from the mucosal homogenates was small, being less than 1% of the dose in all regions. By adding cyclosporine A, fexofenadine disappearance was significantly increased to 18.3% in the ileal region, and slightly but not significantly increased in the jejunal region. However, cyclosporine A did not alter fexofenadine disappearance in the duodenal region. No significant changes in fexofenadine disappearance occurred in the three regions in the presence of ketoconazole, probenecid or mitoxantron (Table 1).

3.2. Permeation of fexofenadine across rat ileal segments

Fig. 1 shows M-to-S and S-to-M permeation of fexofenadine across rat ileal segments for 120 min. The S-to-M permeation of fexofenadine was much greater than the M-to-S permeation. The permeation rate of fexofenadine in the S-to-M direction

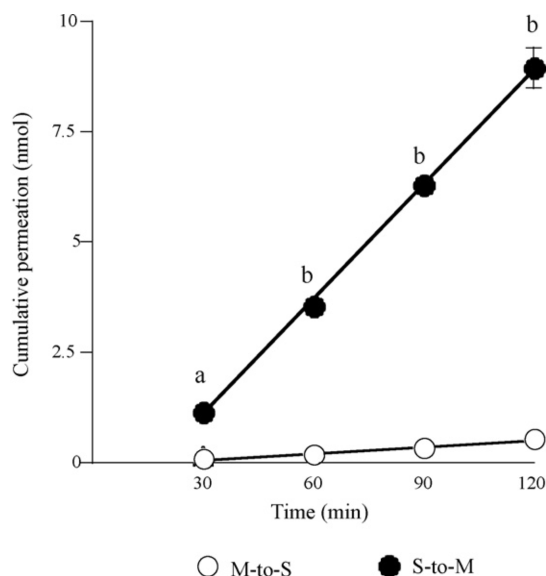

Fig. 1. Mucosal-to-serosal (M-to-S) and serosal-to-mucosal (S-to-M) permeation of fexofenadine across rat ileal segments. Ileal segments (approximately 4 cm in length) were mounted onto diffusion cells and 7 ml of fexofenadine solution (0.5 mM) was introduced into either the mucosal or serosal compartment. At designated time points, 0.5 ml of sample solution was taken from the receiver compartment for drug assay. Each point represents the mean ± S.E. of 3–4 experiments. [a]$p < 0.05$, [b]$p < 0.01$, significantly different from M-to-S.

was approximately 18-fold greater than that in M-to-S direction (Table 2). The S-to-M permeation of fexofenadine was significantly decreased to similar degrees in the presence of cyclosporine A and ketoconazole, whereas the M-to-S permeation of fexofenadine was markedly greater in the presence of cyclosporine A than in the presence of ketoconazole. These changes in fexofenadine permeation in the presence of cyclosporine A and ketoconazole decreased the S-to-M/M-to-S ratios to 3.3 and 6.3, respectively. On the other hand, probenecid did not modulate the fexofenadine permeation in either direction. Also, there were no significant changes in the S-to-M permeation of fexofenadine in the presence of PAH or benzylpenicillin (data not shown).

3.3. Plasma concentration profiles for fexofenadine after intraluminal administration to rats

Fig. 2 shows plasma concentration profiles for fexofenadine, which was administered alone or together with cyclosporine A into entire small intestinal loops at a concentration of 0.1 or 0.5 mM.

Table 1
Effect of various transporter inhibitors on the disappearance of fexofenadine from three regions of the rat small intestine

	Percentage disappearance over 30 mim		
	Duodenum	Jejunum	Ileum
Fexofenadine alone	13.7 ± 3.7	7.0 ± 1.1	3.7 ± 1.7
+Cyclosporine A (20 μM)	13.0 ± 1.0	18.1 ± 9.3	18.3 ± 2.4[a]
+Ketoconazole (50 μM)	10.2 ± 3.2	7.1 ± 3.0	9.9 ± 2.9
+Probenecid (1 mM)	20.8 ± 10.4	7.9 ± 3.2	6.8 ± 2.2
+Mitoxantron	13.9 ± 3.6	9.7 ± 4.2	3.5 ± 1.6

Three loops (each 10 cm in length) were prepared in the duodenal, jejunal, and terminal ileal portions of a rat and 1 ml of fexofenadine solution (0.1 mM) was introduced into the loops. Loop contents were collected after 30 min and the amount of fexofenadine remaining in the contents was determined by HPLC. Data are expressed as the mean ± S.E. of 4–5 experiments.
[a] $p < 0.01$, significantly different from fexofenadine alone.

Table 2
Fexofenadine permeation across rat ileal segments in the presence of various transporter inhibitors

	Permeation rate (nmol/min)		
	M-to-S	S-to-M	S-to-M/M-to-S
Fexofenadine alone	0.005 ± 0.001	0.087 ± 0.004	17.7
+Cyclosporine A (20 μM)	0.017 ± 0.005[a]	0.054 ± 0.004[b]	3.3
+Ketoconazole (50 μM)	0.008 ± 0.001	0.051 ± 0.007[b]	6.2
+Probenecid (1 mM)	0.005 ± 0.001	0.092 ± 0.009	17.1

Ileal segments (approximately 4 cm in length) were mounted onto diffusion cells and drug solution (0.5 mM) was introduced into either the mucosal or serosal compartment. At designated time points, 0.5 ml of sample was taken from the receiver compartment for drug assay. Permeation rates were calculated from the slope of the cumulative amount permeated *vs.* time plot. M-to-S and S-to-M represents mucosal-to-serosal and serosal-to-mucosal permeation, respectively. Data are expressed as the mean ± S.D. of 3–4 experiments.
[a] $p < 0.05$, significantly different from fexofenadine alone.
[b] $p < 0.01$, significantly different from fexofenadine alone.

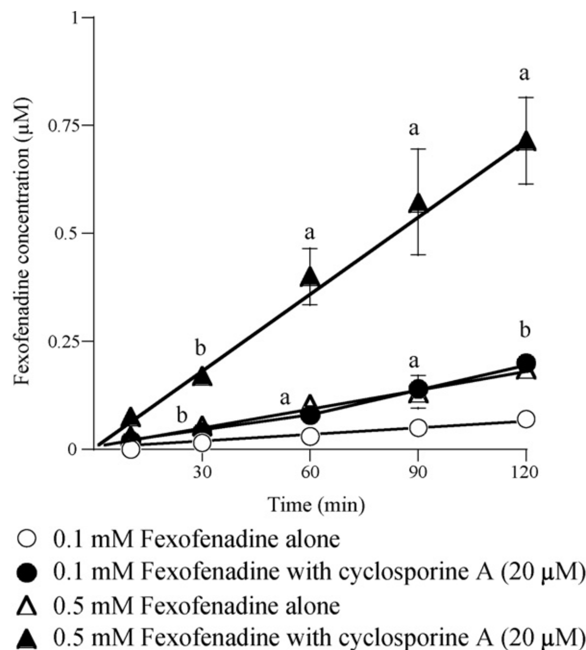

Fig. 2. Plasma concentrations of fexofenadine after its intraluminal administration to rats with or without cyclosporine A (20 μM). A 60-cm loop was prepared in the small intestine of a rat and 6 ml of fexofenadine solution (0.1 or 0.5 mM) was introduced by syringe. At designated time points, blood (0.5 ml) was taken for determining plasma concentration of fexofenadine. Each point represents the mean ± S.E. of 3–4 experiments. [a]$p < 0.05$, [b]$p < 0.01$, significantly different from fexofenadine alone.

Plasma concentrations after administration of 0.1 mM fexofenadine increased linearly up to 120 min and reached 0.07 μM at the end of the experiments. Concurrent administration of cyclosporine A significantly increased the plasma concentrations of fexofenadine at each sampling time point, and the AUC was 280% of that in the absence of cyclosporine A (Table 3). The disappearance of 0.1 mM fexofenadine from the entire small intestinal loops increased from 10 to 27% after 120 min in the presence of cyclosporine A (Table 4).

When fexofenadine was introduced into the entire small intestinal loops at a concentration of 0.5 mM, plasma concentrations again linearly elevated up to 120 min and reached 0.19 μM (Fig. 2). The value was approximately 2.7-fold greater than that obtained after the administration of 0.1 mM fexofenadine. The addition of cyclosporine A again significantly increased fexofenadine concentration at each sampling time point, and the AUC was approximately 3.8-fold that of fexofenadine alone (Table 3). The disappearance of 0.5 mM fexofenadine after 120 min was 4.5% of the dose, which is a smaller percentage than that after the administration of 0.1 mM fexofenadine (Table 4). This value increased to 25.6% in the presence of cyclosporine A.

Table 3
AUC_{0-120} after intraluminal administration of fexofenadine to rats in the absence and presence of cyclosporine A

	AUC_{0-120} (μmol min/l)	
	Alone	+Cyclosporine A (20 μM)
0.1 mM fexofenadine	3.9 ± 0.6	10.9 ± 1.2 (279%)[a]
0.5 mM fexofenadine	11.8 ± 3.0	45.2 ± 7.2 (383%)[a]

A 60-cm loop was prepared in the small intestine of a rat and 6 ml of drug solution was introduced in it. At designated time points, blood (0.5 ml) was taken for determining the plasma concentrations of fexofenadine. Data are expressed as the mean ± S.E. of 3 experiments.

[a] $p < 0.05$, significantly different from fexofenadine alone.

Table 4
Disappearance of fexofenadine from rat entire small intestinal loops in the absence or presence of cyclosporine A

	Percent of disappearance for 120 mm	
	Alone	+Cyclosporine A (20 μM)
0.1 mM fexofenadine	10.1 ± 4.2	26.9 ± 2.2 (266%)[a]
0.5 mM fexofenadine	4.5 ± 3.1	25.6 ± 7.0 (568%)[a]

A 60-cm loop was prepared in the small intestine of a rat and 6 ml of drug solution was introduced. Loop contents were collected after 120 min and the amount of fexofenadine remaining in the contents was determined by HPLC. Data are expressed as the mean ± S.E. of 3 experiments.

[a] $p < 0.01$, significantly different from fexofenadine alone.

4. Discussion

In order to assess to what degree fexofenadine absorption is suppressed by secretory transporters expressed in the intestinal lumen, the changes in fexofenadine absorption in the presence of specific transporter inhibitors were first determined using an in situ loop technique. When fexofenadine was administered alone, relatively small disappearance was noted in the duodenal, jejunal and ileal regions (Table 1). A significant increase in fexofenadine disappearance in the presence of cyclosporine A occurred in the ileal region but not in the duodenal or jejunal regions. As P-gp expression gradually increases from the upper to the lower small intestine (Takara et al., 2003), a possible explanation was that P-gp interfered with the fexofenadine absorption preferentially in the ileal region. On the other hand, ketoconazole, another P-gp modulator (Kageyama et al., 2005), failed to increase fexofenadine disappearance in the rat small intestine including the ileal region (Table 1). This result is in agreement with previous results that ketoconazole did not influence fexofenadine absorption in humans (Tannergren et al., 2003a,b). As ketoconazole is capable of inhibiting OATP as well as P-gp (Cvetkovic et al., 1999), it seemed possible that the lack of increase in fexofenadine disappearance in the presence of ketoconazole resulted from the dual effect of ketoconazole on P-gp and OATP. To elucidate the involvement of mrp2 and bcrp in limiting fexofenadine absorption in rats, the changes in fexofenadine disappearance were next determined in the presence of probenecid, a mrp2 inhibitor (Naruhashi et al., 2002), and mitoxantrone, a bcrp inhibitor (Volk and Schneider, 2003). However, these drugs did not exhibit any modulating effect on fexofenadine disappearance in the three intestinal regions, suggesting that neither mrp2 nor bcrp are related to the low absorption of fexofenadine in rats.

Separately we investigated the log partition coefficient of fexofenadine between *n*-octanol and Tyrode's solution (pH 6.5) and found the value to be 0.23. Taking this into consideration, fexofenadine disappearance seemed to be low even allowing for the fact that cyclosporine A efficiently inhibited P-gp. In order to characterize the movement of fexofenadine in the rat intestine further, in vitro fexofenadine permeation was investigated using rat ileal segments. The permeation rate of fexofenadine was approximately 18-fold greater in the S-to-M direction than in the M-to-S direction (Table 2), indicating extremely secretory-oriented permeation of fexofenadine. The addition of cyclosporine A increased the M-to-S permeation rate of fexofenadine across the rat ileal segments, and extensively lowered its S-to-M permeation rate (Table 2). As a result, the S-to-M/M-to-S ratio shifted from 18 to 3.3. The S-to-M/M-to-S ratio also changed to 6.3 in the presence of ketoconazole. This ketoconazole-induced change resulted from a

significant decrease in the S-to-M permeation rate and an increase in the M-to-S permeation rate that was not as evident in the presence of ketoconazole. The small increase in M-to-S permeation of fexofenadine in the presence of ketoconazole might be attributed to the above-mentioned dual effect on P-gp and OATP. If so, the significant increase in M-to-S permeation of fexofenadine in the presence of cyclosporine A implies that the immunosuppressant influences OATP-mediated fexofenadine transport to lesser extent than ketoconazole. The observation that the secretory-oriented permeation of fexofenadine persisted in the presence of cyclosporine A may raise the possibility that an efflux transporter, which was not modulated by cyclosporine A, was further involved in the secretory transport of fexofenadine across the ileal segments.

Previously, Kikuchi et al. (2006) reported that the permeation of fexofenadine across rat jejunal segments was slightly but significantly greater in the M-to-S than in the S-to-M direction, which is inconsistent with our present results obtained from ileal segments. It has been reported that there are no remarkable regional differences in the expression of OATP in the small intestine (Englund et al., 2006) but that P-gp expression is lower in the upper small intestine that in the lower small intestine (Takara et al., 2003). Therefore, a possible explanation might be that the relative contribution of OATP to the absorptive movement of fexofenadine was greater in the jejunum than in the ileum.

The results obtained here suggest that cyclosporine A is capable of influencing the pharmacokinetics of fexofenadine in vivo. In order to assess the possibility, we evaluated the plasma concentrations of fexofenadine after its administration alone or together with cyclosporine A to the entire small intestinal loops in rats. The plasma concentrations of fexofenadine linearly increased up to 120 min when either 0.1 or 0.5 mM fexofenadine solution was administered. The concurrent administration of cyclosporine A significantly increased the plasma concentration of fexofenadine at each sampling time point. One explanation for these results was that the absorption of fexofenadine increased through the inhibition of secretory transporters sensitive to cyclosporine A.

It is expected that the plasma concentration and AUC of a drug, which is absorbed preferentially by passive diffusion without extensive secretion and first-pass metabolism, would be proportional to dose in most cases. In the present study, the plasma concentration of fexofenadine at 120 min after administration of 0.5 mM fexofenadine was 2.7-fold greater than that of 0.1 mM fexofenadine. Moreover, when 0.5 mM fexofenadine was administered, the percentage that disappeared from loops after 120 min tended to decrease compared with that when 0.1 mM fexofenadine was administered. The dose-dependent decrease in fexofenadine disappearance was possibly due to the saturations of OATP-mediated absorption (Nozawa et al., 2004; Kikuchi et al., 2006). In the presence of cyclosporine A, the magnitude of the increase in the AUC after administration of 0.5 mM fexofenadine was much greater than that after the administration of 0.1 mM fexofenadine. These results suggest that the saturation of OATP enables secretory transporters to restrict fexofenadine absorption more extensively and, therefore, the plasma concentration of fexofenadine was markedly increased due to the potent inhibition of the secretory transporters by cyclosporine A.

In conclusion, the present study demonstrates that intestinal absorption of fexofenadine is relatively small in rats. This is possibly due to potent P-gp-mediated secretory transport of fexofenadine, which is far superior to absorptive transport by OATP.

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