Regular Article

Transporter-mediated Intestinal Absorption of Fexofenadine in Rats

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Summary: Both influx and efflux transporters are thought to be involved in the intestinal absorption of fexofenadine. The present study examined the influx transporter-mediated intestinal absorption of fexofenadine in rats, focusing on the role of rat oatp3 (Oatp1a5). The intestinal permeability of fexofenadine was evaluated by means of the Ussing chamber method in the presence of a P-glycoprotein inhibitor to block efflux transport. The permeability of fexofenadine from the mucosal to the serosal side was higher than that from the serosal side to the mucosal side. Transport of fexofenadine was saturable, and was significantly decreased by an organic anion transporting polypeptide (oatp) inhibitor. Furthermore, uptake of fexofenadine by Xenopus oocytes expressing rat oatp3 was significantly greater than that by water-injected oocytes, and the affinity of oatp3 for fexofenadine (Km) was about 60 µM, which is comparable with the value obtained by the Ussing chamber method using rat intestinal tissues. These results indicate that oatp3 plays a role as an influx transporter in the intestinal absorption of fexofenadine in rats.

Key words: fexofenadine; transporter; absorption; rat; OATP; intestine

Introduction

Fexofenadine is a hydrophilic (log P = 0.30), non-sedating histamine H1-receptor antagonist, which is active after oral administration (product information, Aventis Pharmaceuticals, Inc.). Coadministration of erythromycin (500 mg three times a day) or ketoconazole (400 mg once daily) with fexofenadine results in a substantial increase in the steady-state plasma concentration of fexofenadine and its plasma AUC by 109% or 164%, respectively (product information, Aventis Pharmaceuticals, Inc.). This observation may be explained by the involvement of efflux transport via P-glycoprotein in the fexofenadine absorption process.1-3) It is also known that the intestinal absorption of fexofenadine in humans is decreased in the presence of fruit juices that may contain intestinal influx transporter inhibitors.4-6) In those studies, an increase of the concentration of the fruit juices led to a decreased bioavailability of fexofenadine in humans, and a normal concentration of fruit juice at high volume also led to a decrease of the oral bioavailability of fexofenadine in humans and rats.6,7) These results imply a key role of influx transporter(s) in fexofenadine absorption. Fexofenadine is a substrate of organic anion transporting polypeptides (OATP/oatps), such as human OATP1A2, OATP2B1, and OATP1B3 and rat oatp1 (1a1), oatp2 (1a4), and oatp3 (1a5).2,4,9) Recently, we reported that OATP2B1 is localized at the apical membrane of human small intestinal epithelial cells9) and we showed that fexofenadine was transported by OATP2B1 in transfected cells.10) However, oatp3 is expressed at the apical membrane of rat small intestine11) and fexofenadine is a substrate of oatp3.4) The decrease of fexofenadine absorption in humans upon coadministration with fruit juices, mentioned above, may be explained by the inhibition of OATP-mediated influx by components of the fruit juices. Very recently, it was also reported that fruit juices reduced the transport of estrone-3-sulfate mediated by OATP2B1 in in vitro experiments.12) Accordingly, it is possible that OATP1B2 or other similar transporters are involved in the influx process of fexofenadine and their function is inhibited by constituents of fruit juices. However, there is a species difference in OATP/oatp transporters and the participation of OATP2B1 in human intestinal absorption is difficult to clarify in vivo. Thus, animal experiments using both in vitro and in vivo methods should be useful to clarify the mechanism of transporter-mediated absorption.
intestinal absorption of fexofenadine. The counterpart of OATP2B1 in rats is not clear, but oatp3 in rats is expressed at the apical membrane of rat small intestinal epithelial cells\(^{(1)}\) and can transport fexofenadine in \textit{in vitro} transfected cells,\(^{(4)}\) though the transport characteristics of oatp3-mediated transport of fexofenadine have not been examined in detail. Accordingly, in the present study, we investigated the influx transporter-mediated intestinal absorption of fexofenadine in rats using rat intestinal tissues and compared the transport characteristics with those of oatp3 to evaluate the contribution of OATP/oatp transporters to the intestinal absorption of fexofenadine.

**Materials and Methods**

**Materials:** Fexofenadine hydrochloride was purchased from Toronto Research Chemicals Inc. (North York, Canada). Ketoconazole was purchased from Wako Pure Chemical Industries (Osaka, Japan). Estrone-3-sulfate, potassium salt was purchased from Sigma-Aldrich (St. Louis, MO). \[^3H\]Estrone-3-sulfate, ammonium salt (2120 GBq/mmol) was purchased from PerkinElmer Life and Analytical Sciences (Boston, MA). \[^{14}C\]Inulin carboxyl (92.5 MBq/g) was purchased from American Radiolabeled Chemicals (St. Louis, MO). All other reagents were purchased from Sigma-Aldrich and Wako Pure Chemical Industries Ltd.

**Transport experiments by the Ussing-type chamber method:** Rat intestinal tissue sheets were prepared as described previously.\(^{(13)}\) Male Wistar rats (8 or 9 weeks, Saitama Experimental Animals Supply Co., Ltd. (Saitama, Japan)) were anesthetized with urethane and a segment of jejunum was removed. The tissue was rapidly stripped of serosal muscle layers, and mounted vertically in an Ussing-type chamber that provided an exposed area of 0.5 cm\(^2\). The volume of bathing solution on each side was 4.5 mL, and the temperature was maintained at 37°C. The transport medium consisted of 128 mM NaCl, 5.1 mM KCl, 1.4 mM CaCl\(_2\), 1.3 mM MgSO\(_4\), 21 mM NaHCO\(_3\), 1.3 mM KH\(_2\)PO\(_4\), 10 mM NaH\(_2\)PO\(_4\), and 5 mM glucose at pH 7.4 and was gassed with 100% O\(_2\) before and during the transport experiments. In the inhibition studies, the inhibitors, ketoconazole (50 \(\mu\)M) and/or estrone-3-sulfate (1 mM) were added to both the mucosal and serosal chambers. Glass test tubes were used for the experiments to avoid adsorption of fexofenadine on the container. For quantitation of fexofenadine, high-performance liquid chromatography (HPLC) was used as described below. For estimation of paracellular permeability, \[^{14}C\]Inulin was used. Radioactivity was measured with a liquid scintillation counter (LSC-5100, Aloka, Tokyo) using Cleasol-1 as a liquid scintillation fluid (Nakalai Tesque, Kyoto, Japan).

Transport was estimated in terms of permeation (microliters per square centimeter), obtained by dividing the amount transported (micromoles per square centimeter) by the initial concentration of test compound on the donor side (micromoles per microliter). The permeability coefficient (in units of micrometers per square centimeter per minute; centimeters per second) was obtained from the slope of the linear portion of plots of permeated amount against time. Measurements were made at 60, 80, 100 and 120 min.

**Transport experiments in \textit{Xenopus} oocytes expressing oatp3:** The oatp3 cDNA was PCR-amplified using rat intestinal cDNA as a template, with upstream primer 5'-tccaagcttgggagacacagaaaaag-3' and downstream primer 5'-agaattcagatcgtcaccagggcagtag-3', based on the reported oatp3 cDNA sequence\(^{(11)}\) (GeneBank accession #AF083469). A major 2.0-kilobase polymerase chain reaction product was digested with HindIII and EcoRI, and ligated into the expression gene vector pGEMHE, which was kindly provided by Dr. ER Liman.\(^{(14)}\) Complementary RNA (cRNA) of oatp3 was prepared by \textit{in vitro} transcription using T7 RNA polymerase in the presence of ribonuclease inhibitor and RNA cap analog using a mMESSAGEmACHINE kit (Ambion, Austin, TX). Uptake experiments were conducted as described previously.\(^{(15)}\) Briefly, for standard experiments, defolliculated oocytes were injected with 50 nL of water containing 50 ng of cRNA, cultured for 3 days at 18°C in modified Barth’s solution (96 mM NaCl, 1 mM KCl, 2.4 mM NaHCO\(_3\), 0.82 mM MgSO\(_4\), 0.33 mM Ca(NO\(_3\))\(_2\), 0.41 mM CaCl\(_2\) and 10 mM 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid (HEPES) adjusted to pH 7.4) and used for uptake experiments. Uptake was initiated by incubating the oocytes at room temperature in modified Barth’s solution containing a test compound. At appropriate times, the oocytes were washed with ice-cold modified Barth’s solution to terminate the uptake. For quantitation of test compounds, the oocytes were solubilized in 5% sodium dodecyl sulfate solution in the case of radioactive compound ([\(^3H\)]estrone-3-sulfate). For non-radioactive compounds, the oocytes were homogenized by sonicating in 0.1 mL of modified Barth’s solution, mixed with an equal volume of methanol, and centrifuged at 7000 rpm for 10 min. The resultant supernatant was analyzed by HPLC as described below. For the assay of background uptake by the oocytes, the same volume of water without any cRNA was injected into oocytes, which were cultured in modified Barth’s solution, and the uptake was quantitated in the same manner as described above. The uptakes were expressed as the cell-to-medium ratio calculated by dividing the cellular uptake amount by the concentration of test compound in the uptake medium.

**Analytical methods:** Fexofenadine was quantified by means of HPLC using a reversed-phase analytical
column ODS 80Ts (4.9×150 mm; Tosoh, Tokyo, Japan) with acetonitrile/methanol/12 mM ammonium acetate (19:29:52) as the mobile phase at a flow rate of 1.0 mL/min with a constant flow pump (PU-2089 plus; JASCO). The analytical column was kept at 40°C, and the eluent was monitored with a fluorescence detector (FP-2025 plus; JASCO) at excitation and emission wavelengths of 240 and 290 nm, respectively. The retention time of fexofenadine was approximately 10 min. To estimate kinetic parameters for saturable transport, the initial uptake rate (v) was fitted to the following equation by nonlinear least-squares regression analysis using KaleidaGraph (Synergy Software, Reading, PA).

\[ v = \frac{V_{\text{max}} \times s}{(K_m + s)} + kd \times s \]

where v and s are the uptake rate and concentration of substrate, respectively, and \( K_m \), \( V_{\text{max}} \) and kd represent the half-saturation concentration (Michaelis constant), the maximum transport rate, and the apparent non-saturable first-order rate constant, respectively. All data were expressed as means ± S.E.M., and statistical analysis was performed by the use of Student’s t test with p<0.05 as the criterion of significance.

**Results**

**Effect of P-glycoprotein inhibitor on permeability of fexofenadine:** It was reported that P-glycoprotein is involved in efflux transport of fexofenadine in the intestine.\(^2\) Because the purpose of the present study is to evaluate the influx transport process of fexofenadine, an inhibitor of P-glycoprotein was used in order to highlight the influx process. Since 50 μM ketoconazole was shown to inhibit P-glycoprotein in the same intestinal chamber method.\(^16\) We also used 50 μM ketoconazole as the P-glycoprotein inhibitor. The mucosal-to-serosal permeability of fexofenadine was significantly increased from 2.24±0.11 to 3.49±0.19×10⁻⁶ cm/sec in the presence of ketoconazole, in the upper region of the small intestine (Table 1). In the lower region of the small intestine, a similar increase of the permeability from 1.75±0.07 to 4.56±0.26×10⁻⁶ cm/sec was observed (Table 1).

Table 1. Effects of ketoconazole and estrone-3-sulfate on permeability of fexofenadine and [¹⁴C]inulin across rat intestinal tissues

<table>
<thead>
<tr>
<th>Compound</th>
<th>Inhibitor</th>
<th>Permeability (×10⁻⁶ cm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Upper</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>None</td>
<td>2.24 + 0.11</td>
</tr>
<tr>
<td></td>
<td>+ Ketoconazole</td>
<td>3.85 + 0.31*</td>
</tr>
<tr>
<td></td>
<td>+ Ketoconazole + Estrone-3-sulfate</td>
<td>2.35 + 0.15†</td>
</tr>
<tr>
<td>[¹⁴C]Inulin</td>
<td>None</td>
<td>1.74 + 0.24</td>
</tr>
<tr>
<td></td>
<td>+ Ketoconazole</td>
<td>1.79 + 0.28</td>
</tr>
</tbody>
</table>

Fexofenadine transport was measured in the absence of inhibitor or in the presence of ketoconazole (50 μM) alone or with estrone-3-sulfate (1 mM). [¹⁴C]Inulin transport across rat intestinal tissue was measured in the absence or presence of ketoconazole (50 μM). Transport of fexofenadine and [¹⁴C]inulin across the intestinal tissue was evaluated from the time course of the transport by the Ussing chamber method as described in the text. The permeability was measured using isolated tissues from upper and lower regions of rat small intestine. The experimental solution was adjusted to pH 7.4 and the temperature was maintained at 37°C. Each value represents the mean ± S.E.M. (n=6–12). (*) indicates a significant difference of the permeability in the presence of ketoconazole from that in its absence. (†) indicates a significant difference of the permeability in the presence of ketoconazole and estrone-3-sulfate from that in the presence of ketoconazole alone (p<0.05). N.T.: not tested.

**Permeability of fexofenadine across the intestinal tissues:** To examine whether an influx transporter is associated with apical uptake of fexofenadine, the permeability of fexofenadine was measured in the mucosal-to-serosal and serosal-to-mucosal directions in the presence of ketoconazole. The permeability of fexofenadine in the mucosal-to-serosal direction (3.49±0.19×10⁻⁶ cm/sec) was significantly higher than that in the serosal-to-mucosal direction (2.82±0.15×10⁻⁶ cm/sec), as shown in Fig. 1. To characterize further the

![Fig. 1. Permeability of fexofenadine (50 μM) across isolated rat intestinal tissues.](image)
influx transporter, the concentration dependence of the permeability of fexofenadine was examined in the concentration range of 50–500 μM. As shown in Fig. 2, the permeability decreased with increasing concentration from 50 to 100 μM, but no further decrease in permeability was observed at higher concentrations. Although we could not evaluate the permeability at lower concentrations to obtain kinetic parameters, because of the detection limit of fexofenadine, the results apparently suggested that $K_m$ of fexofenadine is of the order of ten μM in rat small intestine (Fig. 2).

**Effect of oatp inhibitor on transport of fexofenadine:**

We investigated the involvement of oatp3 in intestinal absorption of fexofenadine, because oatp3 transports fexofenadine and is expressed at the apical membrane of rat small intestine. First of all, we examined the selective expression of oatp3 in rat small intestinal tissues. RT-PCR was used to investigate the expression of oatps in the rat small intestine and liver. mRNA expression of oatp1, 2, and 4 was observed in rat liver, but not in rat small intestine. In contrast, oatp3 was clearly detected in small intestine, but it was not detected in liver (data not shown). Then we examined the inhibitory effect of an oatp substrate on the transport of fexofenadine across the rat small intestinal tissues. Since estrone-3-sulfate is a good substrate of various OATPs/oatps, it was used. The permeability of fexofenadine in the mucosal-to-serosal direction was significantly decreased in both the upper and lower regions of small intestine in the presence of 1 mM estrone-3-sulfate (Table 1).

**Transport characteristics of oatp3 for fexofenadine:**

Involvement of oatp3 in the transport of fexofenadine in small intestine was further assessed by measuring the effect of increasing concentrations of fexofenadine on the transport of [3H]estrone-3-sulfate by oatp3 expressed in *Xenopus* oocytes. As shown in Fig. 3, the evaluated 50% inhibitory concentration of fexofenadine (IC$_{50}$) was 25.4 ± 4.0 μM. In addition, the concentration dependence of fexofenadine transport by oatp3 was clearly detected in small intestine, but it was not detected in liver (data not shown). Then we examined the inhibitory effect of an oatp substrate on the transport of fexofenadine across the rat small intestinal tissues. Since estrone-3-sulfate is a good substrate of various OATPs/oatps, it was used. The permeability of fexofenadine in the mucosal-to-serosal direction was significantly decreased in both the upper and lower regions of small intestine in the presence of 1 mM estrone-3-sulfate (Table 1).

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**Fig. 2.** Concentration dependence of fexofenadine transport across upper small intestine of rats.

Fexofenadine transport from the mucosal side to the serosal side was measured at concentrations of 50 to 500 μM in the presence of ketoconazole (50 μM). The experimental solution was adjusted to pH 7.4 and the temperature was maintained at 37°C. Each point represents the mean ± S.E.M. (n = 4–12).

**Fig. 3.** Inhibitory effect of fexofenadine on oatp3-mediated uptake of [3H]estrone-3-sulfate by *Xenopus* oocytes.

Uptake of [3H]estrone-3-sulfate (10 nM) by *Xenopus* oocytes injected with cRNA of oatp3 was measured at 25°C and pH 7.4 for 30 min. The results are shown as a percentage of control uptake measured in the absence of fexofenadine after subtracting the uptake of water-injected oocytes. Concentrations of fexofenadine were in the range from 5 to 1000 μM. Each result represents the mean ± S.E.M. (n = 5–9).

**Fig. 4.** Concentration dependence of fexofenadine uptake by oatp3-expressing *Xenopus* oocytes.

Uptake of fexofenadine by *Xenopus* oocytes injected with cRNA of oatp3 was measured at 25°C and pH 7.4 for 120 min. The concentration of fexofenadine ranged from 3 to 1000 μM. Each result represents the mean ± S.E.M. (n = 5).
examined by using oatp3-expressing Xenopus oocytes. The uptake of fexofenadine was saturable with $K_m$ and $V_{max}$ values of $59.1 \pm 18.8 \mu M$ and $57.8 \pm 4.7$ pmol/oocyte in 120 min (Fig. 4).

**Discussion**

The purpose of the present study was to examine the involvement of influx transporter(s) in the intestinal absorption of fexofenadine in rats. Several previous studies have suggested that OATP-like transporters could be involved in the absorption of fexofenadine.\(^{2,4-9}\) It was shown that human OATP2B1 (OATP-B) transports various organic anions, including fexofenadine, in a pH dependent manner in our study using OATP2B1-transfected cells.\(^{10}\) Furthermore, intestinal absorption of fexofenadine is reduced by coadministration of fruit juices,\(^{4-6}\) components of which reduce the transport of fexofenadine in rats, it is necessary to compare the intestinal transport of fexofenadine in rats, with a greater ratio of increase in the lower region of the small intestine (Table 1). Since P-glycoprotein expression is greater in the lower region of small intestine than in the upper region,\(^{20,21}\) the above observation can be explained by the inhibition of P-glycoprotein-mediated efflux of fexofenadine by ketoconazole. Therefore, ketoconazole can be used to highlight the influx transport of fexofenadine across the small intestine.

The higher mucosal-to-serosal permeability of fexofenadine in the presence of ketoconazole (Fig. 1), the saturability of absorptive permeability (Fig. 2), and the significant reduction of fexofenadine transport in the presence of estrone-3-sulfate (Table 1) all strongly suggest that an influx transporter, such as oatp, is involved. We used estrone-3-sulfate at 1 mM to inhibit oatps, since estrone-3-sulfate exhibited $K_m$ values of 4.5–11, 11, 268 and 37 $\mu M$ for oatp1, 2, 3, and 4, respectively.\(^{17}\) In the inhibition study by estrone-3-sulfate, the decrements were comparable for upper and lower regions, showing 1.50 and $1.34 \times 10^{-6}$ cm/sec, respectively. Therefore, it was considered that there is no regional difference in transport activity of influx transporter, which can be inhibited by estrone-3-sulfate, between upper and lower regions. Since there is the report that oatp3 mRNA was expressed at similar levels down the length of the small intestine,\(^{13}\) the present observation is consistent with the lack of regional difference of oatp3 expression level. On the other hand, there was regional difference in the permeability in the presence of both of ketoconazole and estrone-3-sulfate between upper and lower regions. At lower region, the permeability in the presence of those two inhibitors ($3.22 \times 10^{-6}$ cm/sec) was significantly higher than that in the absence of them ($1.75 \times 10^{-6}$ cm/sec), while those permeabilities at upper region were comparable (2.24 and $2.35 \times 10^{-6}$ cm/sec). This regional difference may be explained by the higher expression of efflux transporter P-gp\(^{20,23}\) and/or the contribution of unknown influx transporter that cannot be inhibited by estrone-3-sulfate at lower part of small intestine. The mucosal-to-serosal permeability was saturated at about 0.1 mM (Fig. 2). Because of the detection limit of the quantitation, we were unable to obtain an exact $K_m$ value, but this observation suggested that fexofenadine has a $K_m$ value lower than 0.1 mM. The affinity of fexofenadine for the intestinal influx transporter is close to the $K_m$ values of fexofenadine uptake by oatp1 (32 $\mu M$) and oatp2 (6.0 $\mu M$) expressed in HeLa cells (2) and
the $K_m$ value of oatp3 obtained in the present study (59 
$\mu$M) (Fig. 4). Furthermore, the IC$_{50}$ of fexofenadine on 
aotp3-mediated transport of estrone-3-sulfate was 
similar to the $K_m$ of fexofenadine transport by rat oatp3. 
All of these observations are consistent with the 
theory that rat oatp3 is involved in the intestinal 
absorption of fexofenadine in rats.

In conclusion, by evaluating the intestinal transport 
of fexofenadine in the rat intestinal tissues in the 
presence of a P-glycoprotein inhibitor, we could clearly 
observe saturable absorptive transport of fexofenadine. 
Furthermore, the affinity of fexofenadine transport 
across rat intestinal tissues was comparable with the $K_m$ 
value of fexofenadine for rat oatp3. These results 
provide strong evidence that fexofenadine is absorbed 
via oatp3 in rats. Since OATP1A2 was recently reported 
to transport fexofenadine and to be expressed in human 
small intestinal tissues, like OATP2B1, further studies 
on the mechanism of human intestinal absorption 
of fexofenadine, based on these animal experimental 
observations, seem to be desirable.

Acknowledgements: We thank Dr. Kazumasa 
Naruhashi for the valuable suggestions and Dr. ER Li-
man for gift of the expression vector pGEMHE. This in-
vestigation was supported by a Grant-in-Aid for Scien-
tific Research from the Ministry of Education, Culture, 
Sports, Science and Technology, Japan.

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