**Regional Difference in P-glycoprotein Function in Rat Intestine**

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**Summary:** It has been reported that inhibition of the P-glycoprotein (P-gp) results in the improved absorption of P-gp substrate in the intestinal tract. In fact, the increased permeability of P-gp substrate across the intestinal epithelium was observed following inhibition of P-gp in *in vitro* experiments. To develop the formulation containing P-gp inhibitor and P-gp substrate for practical use, it is necessary to know whether the results obtained in the *in vitro* experiments are reproducible at whole body level. It is also important to find out the regional difference of the P-gp activity in the intestinal tract. In this study, we examined whether verapamil, a specific inhibitor of P-gp, improves the absorption of rhodamine123 (Rho123), a substrate of P-gp, from the jejunum, ileum, and colon of rats using the *in situ* loop method. The water content in the loop decreased during the experiment, resulting in a significant change of the Rho123 concentration in the loop. Thus, to accurately determine the absorption rate of Rho123, it was necessary to measure the water movement. It was found that there was a regional difference in the water movement, i.e., greatest in colon, followed by ileum. Verapamil did not change the water movement in any intestinal regions. When the concentration of Rho123 in the loop was corrected by water movement, the Rho123 clearance was in the order of ileum (1.15 µL/min/cm), colon (0.83 µL/min/cm) and jejunum (0.47 µL/min/cm). In the presence of verapamil, the Rho123 clearance was significantly increased at jejunum and ileum but not in colon (ileum: 2.08 µL/min/cm, colon: 1.14 µL/min/cm, jejunum: 1.28 µL/min/cm). These results suggest that P-gp inhibits the drug absorption in jejunum and ileum. From these results, it is possible to evaluate the role of P-gp and its regional difference in the *in situ* experiments. In particular, the inhibition of P-gp results in an increase in absorption of the P-gp substrate limited to jejunum and ileum.

**Key words:** P-glycoprotein; jejunum; ileum; colon; water absorption; rhodamine 123; verapamil

**Introduction**

In the development of oral drugs, it has been attempted to improve the intestinal drug absorption by co-administering with absorption enhancers. P-glycoprotein (P-gp) exists in the intestinal epithelial cells and has an affinity to a wide range of substrates to excrete various kinds of drugs into the lumen. P-gp is an important factor which decreases bioavailability of oral drugs, and thus inhibition of P-gp is expected to increase the intestinal absorption of drugs.

Although there are many reports on the effects of inhibition of P-gp on intestinal permeability, most of these experiments were performed using the Ussing-type chamber method with isolated intestinal segments or diffusion-type chamber method with Caco-2 cells, and only a small number of experiments were performed using an *in situ* experimental system.

There are various reports showing the regional difference in the expression and activity of P-gp. The expression of MDR1 mRNA is higher in the lower part of the intestine in humans[^1^] and the expression of mdr1 mRNA in rat intestine is moderate in the duodenum and the jejunum, maximal in the ileum, and becomes lower through the proximal and distal colon.[^2^] On the other hand, the P-gp protein level in the ileum was 2.31-fold higher than that in the jejunum of rats.[^3^] Consistent with these observations, the results obtained in the *in vitro* everted rat small intestine showed that there was a regional variation in the P-gp-mediated rhodamine 123 (Rho123) transport, and the rate of transport from serosal to mucosal in the ileum was higher than that in...
the jejunum.\(^6\) The P-gp-mediated transport of substrates including etoposide,\(^7\) digoxin and vinblastine\(^8\) is reported to be higher in the ileum, whereas the P-gp-mediated secretory flux of quinine is highest in jejunum.\(^7\)

In contrast, measurements of absorption, excretion and clearance of the P-gp substrate including vinblastine,\(^9\) methylprednisolone,\(^9\) ivermectin,\(^10\) talinolol\(^11\) and digoxin\(^12\) indicated that the P-gp-mediated transport was highest in duodenum, jejunum or colon, indicating that this order dissociates from that of P-gp expression level.

The aim of the present experiments was to examine the role of P-gp on the absorption of drugs from intestine in whole body. We used Rho123 as a P-gp substrate and verapamil as a selective inhibitor of P-gp and evaluated the effect of verapamil to increase the absorption of Rho123 at jejunum, ileum and colon using the in situ loop method. Also, we clarified the regional difference in P-gp activity.

**Materials and Methods**

**Materials:** Verapamil hydrochloride, rhodamine-123, FITC-dextran40,000 (FD40) and other drugs were purchased from the Sigma Aldrich Co. Ltd. All other reagents were of analytical grade or better.

**Animal and experimental design:** Male Wistar rats (eight week old) were purchased from Japan SLC Ltd. (Shizuoka, JAPAN). All the animal experiments were performed according to the guideline of Tokyo University of Pharmacy and Life Science. The animals were fasted for 18–20 hours before starting the experiment. Water was freely given while fasting.

Intestinal absorption was evaluated by the Doluisio method.\(^13\) The jejunum, ileum, or colon was exposed by midline abdominal incision. Two L-shaped glass cannulas were inserted through small slits at the proximal and distal ends of the following segments to make a 7-cm loop. The proximal end of the jejunal loop was 10-cm below the Treize ligament. The proximal end of the ileal loop was 12-cm above the ileocecal junction. The proximal end of the colonic loop was 3-cm below the caecum.

Each cannula was secured by ligation with a silk suture, and the intestine was returned to the abdominal cavity to maintain its integrity. A 4-cm silicone tubing was attached to the exposed end of the cannula, and a 10-mL syringe with a hole was attached to the end of the silicone tubing. A 5-mL of dosing solution containing Rho123 or FD40 was administrated via the hole of the syringe into the loop. One-milliliter was then sampled from the loop at 0 and 30 min after administration. The residue was collected at 60 min.

The drugs were dissolved in a modified Krebs-Henseleit bicarbonate buffer solution (KHBB). KHBB is composed of NaCl, 136.89 mM; KCl, 5.00 mM; Na₂HPO₄, 0.95 mM; NaH₂PO₄·2H₂O, 4.85 mM; glucose, 19.45 mM; NaHCO₃, 3.50 mM. KHBB (pH 7.4) was previously aerated for 30 minutes with a gas mixture (95% O₂ and 5% CO₂) at 37°C. Control solution contained 26 μM Rho123, and verapamil was added to this solution to make a final concentration of 0.5 mM or 1 mM. In another series of experiments, 0.1% FD40 was added instead of Rho123 for the measurement of water movement. To examine the effect of preincubation with verapamil on the P-gp function, 2.5 mL verapamil (0.5 mM) was added to the loop and, 60 min later, 2.5 mL Rho123 (52 μM) was also added to make a final Rho123 concentration of 26 μM.

The concentrations of Rho123 and FD40 were measured by a fluorescent spectrophotometer (JASCO FP-6500) at the excitation wavelength of 492 nm and at absorption wavelength of 515 nm for FD40, and at the excitation wavelength of 485 nm and at the absorption wavelength of 546 nm for Rho123.

Changes in water contents were calculated from the changes in FD40 concentration. Tomita et al. (2000) examined the polarized transport of FD4 (m.w. 4,000) and FD70 (m.w. 70,000) across rat colonic membrane and reported that transport of these compounds from mucosal to serosal side of a chamber was very low.\(^14\) Although they did not examine the transport of FD40 (m.w. 40,000), it is reasonable to assume that the transport of FD40 may also be very low because these two compounds have similar chemical structure and similar molecular weight. Based on this assumption we used FD40 concentration in the intestinal loop as an indicator of water absorption. Apparent concentration of Rho123 \(C_{\text{Rho123,app}}\) was adjusted for changes in water content using the following equation, and the actual concentration of Rho123 \(C_{\text{Rho123}}\) was obtained. Values before (A%) and after the adjustment for water contents (C%) are also shown.

\[
\text{Change in water content} (\%) = \left( C_{\text{FD40,60min}} - C_{\text{FD40,0min}} \right) / C_{\text{FD40,60min}} \times 100
\]

\[
C_{\text{Rho123}} (%) = C_{\text{Rho123,app}} (%) \times (100 - \text{Change in water content} (\%)) / 100
\]

The absorption clearance for Rho123 was calculated using \(C_{\text{Rho123}}\) using the following equation.

Disappearance rate (μmol/min) = (100 - \(C_{\text{Rho123}}\ (%)\)) × initial concentration of Rho123 (μM) × volume of solution in lumen (μL)/60 (min)

Absorption clearance (μL/min/cm) = disappearance rate (μmol/min)/initial concentration of Rho123 (μM)/loop length (cm)
**Statistical analysis:** All the results were expressed by mean value ± standard error (Mean ± SE). Statistical significance between two groups was analyzed by using Student’s t-test, and P value less than 0.5% was considered to be significantly different.

**Results**

**Time-course in the change of Rho123 concentration in lumen:** In the jejunum, the concentration of Rho123 in the loop measured 60 min after initiation of the absorption experiment was 103.2 ± 1.9% of the initial concentration under control conditions, the value of which is not significantly different from the initial concentration, indicating that Rho123 was not absorbed from the jejunum (Fig. 1A and Table 1).

When 0.5 mM verapamil was added simultaneously with Rho123, the concentration of Rho123 decreased to 83.8 ± 2.2% at 60 min absorption period, indicating that a significant amount of Rho123 was absorbed from the jejunum (Fig. 1A and Table 1). The effect of 1.0 mM verapamil was not significantly different from that of 0.5 mM, decreasing the concentration of Rho123 to 86.0 ± 3.0% at 60 min (Table 1).

When 0.5 mM verapamil was added 60 min before the addition of Rho123, the concentration of Rho123 was decreased to 76.4 ± 4.1% at 60 min absorption period, the value of which was not significantly different from that obtained by the simultaneous addition of verapamil and Rho123 (83.8%) (Table 1). Although the concentration of Rho123 after pretreatment with verapamil was decreased to 88.0 ± 3.8% at 30 min, no such decrease was observed at 30 min when Rho123 and 1 mM verapamil were added simultaneously (Table 1).

In the ileum, Rho123 concentration in the loop did not change (100.6 ± 6.1% at 60 min) under control conditions (Fig. 1B and Table 1). When 0.5 mM or 1 mM verapamil was added simultaneously with Rho123, the Rho123 concentration was decreased to 87.1 ± 5.6% and 85.6 ± 5.3%, respectively, at 60 min. The effect of 1 mM verapamil, was significantly different from the values in control (Fig. 1B and Table 1).

When 0.5 mM verapamil was added 60 min before the addition of Rho123, the concentration of Rho123 decreased significantly to 73.8 ± 7.8% at 60 min (Fig. 1B and Table 1). This value was not significantly different from that obtained by the simultaneous addition of 0.5 mM verapamil and Rho123. The concentrations of Rho123 did not change at 30 min irrespective of presence or absence of verapamil (Fig. 1B and Table 1).

In colon, the concentration of Rho123 in the loop was unexpectedly increased to 108.2 ± 3.7% and 120.8 ± 7.2% at 30 min and 60 min, respectively (Fig. 1C and Table 1). When 0.5 mM or 1 mM verapamil was added simultaneously with Rho123, the increase in Rho123 concentration was 104.2 ± 6.3% and 107.5 ± 6.0%, respectively. When 0.5 mM verapamil was added 60 min before the addition of Rho123, the Rho123 concentration in the loop was 113.6 ± 9.3% (Fig. 1C and Table 1).

**Measurements of water absorption:** As shown in Fig. 2, time-dependent water absorption was observed in all regions of intestine in the absence of verapamil. The amount of absorption at 60 min was about 12% in jejunum, 24% in ileum and 31% in colon, indicating that a larger amount of water is absorbed at the lower part of the intestine (Fig. 2). In the presence of 1 mM verapamil, absorption of water at 60 min was about 13%, 32% and 28% for jejunum, ileum and colon, respectively, indicating that verapamil did not have any significant effect on water absorption (Table 2).

**Correction of the Rho123 concentrations by water absorption:** After the volume correction, in jejunum, Rho123 concentrations at 60 min in the absence and presence of verapamil were 90.7 ± 1.6% and 74.4 ± 2.6%, respectively (Table 1). In ileum, Rho123
Table 1. Luminal concentration of Rho123 in the presence or absence of verapamil with/without the preloading

<table>
<thead>
<tr>
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<th>Before</th>
<th>After</th>
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<tr>
<td></td>
<td>Time (min)</td>
<td>% of initial concentration</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(% of initial concentration)</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Control</td>
<td>97.9±0.9</td>
</tr>
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<td></td>
<td>Ver 0.5 mM</td>
<td>94.1±4.7</td>
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<td></td>
<td>(co-administration)</td>
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<tr>
<td></td>
<td>Ver 1.0 mM</td>
<td>97.9±1.5</td>
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<tr>
<td></td>
<td>(co-administration)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ver 0.5 mM</td>
<td>88.0±3.8</td>
</tr>
<tr>
<td></td>
<td>(pretreatment)</td>
<td></td>
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<tr>
<td>Ileum</td>
<td>Control</td>
<td>95.5±4.2</td>
</tr>
<tr>
<td></td>
<td>Ver 0.5 mM</td>
<td>100.7±4.5</td>
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<tr>
<td></td>
<td>(co-administration)</td>
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<tr>
<td></td>
<td>Ver 1.0 mM</td>
<td>103.8±6.6</td>
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<td></td>
<td>(co-administration)</td>
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<tr>
<td></td>
<td>Ver 0.5 mM</td>
<td>97.3±7.0</td>
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<td></td>
<td>(pretreatment)</td>
<td></td>
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<tr>
<td>Colon</td>
<td>Control</td>
<td>108.2±3.7</td>
</tr>
<tr>
<td></td>
<td>Ver 0.5 mM</td>
<td>93.5±5.1</td>
</tr>
<tr>
<td></td>
<td>(co-administration)</td>
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<tr>
<td></td>
<td>Ver 1.0 mM</td>
<td>104.2±3.0</td>
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<tr>
<td></td>
<td>(co-administration)</td>
<td></td>
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<tr>
<td></td>
<td>Ver 0.5 mM</td>
<td>99.2±3.4</td>
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<tr>
<td></td>
<td>(pretreatment)</td>
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After 30, 60 min, the luminal concentration of Rho123 was measured. The luminal concentration of FD40 was measured to correct the water movement. The values in Table 1 represent the % of initial concentration “Before” and “After” show the luminal concentration of Rho123 before and after volume correction, respectively. Data represent means and S.E. (n = 4–6 for each condition). *p < 0.05, **p < 0.01 compared with control.

However, Rho123 concentration tended to decrease to 83.5 ± 5.0% in the absence of verapamil and to 77.3 ± 4.3% in the presence of 1 mM verapamil, although the decrease was not statistically significant (Fig. 3C).

Comparison of the clearance: To compare regional difference of effects of verapamil, absorption clearance was calculated from the time-dependent changes in the Rho123 concentration in the loop. Under the control conditions, the absorption clearances in the jejunum, ileum and colon were 0.47, 1.15 and 0.83 µL/min/cm, respectively (Table 2). The difference between jejunum and ileum was statistically significant. On the other hand, in the presence of 1 mM verapamil, the absorption clearances in the jejunum, ileum and colon were increased to 1.28, 2.08 and 1.14 µL/min/cm, respectively (Table 2). The differences (CL_diff) between the clearance values obtained in the absence and in the presence of verapamil (CL_terr – CL_cont) were 0.81, 0.93 and 0.34 µL/min/cm for the jejunum, ileum and colon, respectively, and the difference was statistically significant in both the jejunum and ileum. Furthermore, the ratio of CL_diff to CL_terr was calculated to be 0.63, 0.45 and 0.27, respectively, for the jejunum, ileum and colon.

Fig. 2. Water absorption over intestinal wall for 30 min and 60 min in the absence (open column; 30 min, solid column; 60 min) and presence of 1 mM verapamil (dotted column; 30 min, hatched column; 60 min). Data represents mean ± S.E. (n = 4–6).

Concentrations at 60 min in the absence and presence of verapamil were 77.0 ± 4.7% and 58.4 ± 2.4%, respectively. In colon, in the absence or in the presence of verapamil, Rho123 concentration at 60 min was increased before the correction. After the correction,
Table 2. Effect of verapamil on intestinal clearance of rho123

<table>
<thead>
<tr>
<th></th>
<th>Jejunum</th>
<th>Ileum</th>
<th>Colon</th>
</tr>
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<tbody>
<tr>
<td>CLcont</td>
<td>0.47±0.06</td>
<td>1.15±0.23</td>
<td>0.83±0.32</td>
</tr>
<tr>
<td>CLver</td>
<td>1.28±0.13**</td>
<td>2.08±0.12**</td>
<td>1.14±0.21</td>
</tr>
<tr>
<td>CLdifference = CLver – CLcont</td>
<td>0.81</td>
<td>0.93</td>
<td>0.34</td>
</tr>
<tr>
<td>CLdifference/CLver</td>
<td>0.63</td>
<td>0.45</td>
<td>0.27</td>
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The CLdifference indicates the degree of the P-gp-mediated secretion of Rho123. Therefore CLdifference/CLver means contribution ratio of the P-gp-mediated secretion of Rho123 to total uptake of Rho123 into the intestinal epithelial cells.

CLcont: control; CLver: 1 mM Verapamil; Data represent means and S.E. (n=4–6). **p<0.01 compared with control.

![Graphs showing time courses of rhodamine 123 concentration in intestinal lumen](image)

Fig. 3. Time courses of the decrease in rhodamine 123 concentration in intestinal lumen determined by the Dulosio method after correcting water flux. Symbol: □ control; ○ 1 mM verapamil. Data represents mean ± S.E. (n=4–6). **: P<0.01 compared with control.

(Table 2).

Discussion

We examined the absorption of the P-gp substrate Rho123 from the intestinal loop. There was no change in the Rho123 concentration in the jejunum and ileum, whereas the concentration increased in the colon (Table 1). The only possible explanation for this increase in Rho123 concentration was the decrease in luminal water volume. In fact, the colon is known to be the site of water absorption. 15)

To examine this possibility, we measured the water absorption from the intestinal loop using FD40 as a volume indicator. Water was absorbed not only at the colon but also at the jejunum and ileum (Fig. 2). In the colon, the decrease in water volume in the loop was greater than the decrease in Rho123 concentration, and thus, the luminal concentration of Rho123 was found to increase. These results collectively suggest that it is necessary to precisely measure the changes in water volume in the loop and correct the apparent Rho123 concentrations to estimate the Rho123 absorption from the loop.

Although there was time-dependent water absorption at the jejunum, ileum and colon during the first 30 min (0 to 30 min), it seemed to be greater than that during the later 30 min (30 to 60 min) in the jejunum and ileum, as calculated from the data in Fig. 2. This result may be attributable to an experimental deviation whereas possible change in the integrity of intestinal epithelium during a prolonged incubation period cannot be ruled out. However, we did not examine these possibilities in the present experiment.

Correcting the decrease in water volume in the loop, it was found that the Rho123 concentration in the loop decreased at 60 min in all three regions of the intestine, indicating that Rho123 is absorbed from the intestine. In our unpublished observations using the in vitro diffusion chamber method, in the rat colon the Rho123 transport from the serosal side to the mucosal side was much greater than that of the opposite direction. From this result, evaluation of Rho123 absorption in the colon was expected to be difficult because of the presence of the Rho123 excretion mechanism. In the present in vivo experiment, however, it was possible to detect the absorption of Rho123 under the control conditions. This difference between in vivo and in vitro experiments may be attributable to different methods employed in these two experiments.

The Rho123 absorption clearance was in the order of ileum > colon > jejunum. Existence of such a regional difference suggests either the presence of a transporter...
which distributes unevenly in these regions or the regional difference in the P-gp activity. Rho123 has been shown to be a substrate for P-gp, and it is a lipophilic substance with the octanol-water partition coefficient of 3.4. Lipophilic Rho123 may be transported mainly by a passive transport system. Since Rho123 is a cationic substance, on the other hand, some transporting system for the cationic substrates may be involved in the transport of Rho123. In rat kidney, in fact, the organic cation transporter (OCT) has been suggested to be involved in the Rho123 transport. Furthermore, the OCT family has been shown to be expressed in the rat intestine. Considering the possibility that these transporters are functioning differently in each region of the intestine, it is necessary to take into account the possibility that the absorption of Rho123 observed in the absence of verapamil (CL\text{abs}) is influenced not only by the passive diffusion of Rho123 and its excretion by P-gp, but also the regional difference in the functions of the absorptive transporters.

Using verapamil, we tried to evaluate the function of P-gp. Although there is one report showing that verapamil increased water absorption in the duodenum and jejunum but not in rat colon as measured with \textit{in situ} single-pass perfusion method, in our \textit{in situ} loop method, verapamil did not significantly change the water absorption in all three absorption sites. In the presence of verapamil at 1 mM, the decrease of Rho123 concentration from the intestinal loop was significantly increased in the jejunum and ileum. Since verapamil is a selective inhibitor of P-gp, and also since Rho123 is a substrate for P-gp, the increased absorption of Rho123 is attributable to the inhibition of verapamil to the P-gp-mediated excretion. These results also suggest that the clearance observed in the presence of verapamil (CL\text{ver}) represents the absorption of Rho123 in the absence of P-gp excretion. In contrast, the difference between the clearances obtained in the absence and in the presence of verapamil (CL\text{diff}) represents the P-gp-mediated excretion. Furthermore, the value CL\text{diff}/CL\text{ver} represents the contribution of P-gp on the Rho123 absorption. Comparing the values for CL\text{diff}/CL\text{ver}, it was found that the P-gp-mediated excretion of Rho123 was strongest in jejunum followed by ileum. These effects of verapamil suggested that a modulation of P-gp function with an inhibitor is effective for increasing P-gp substrate absorption at these sites.

We also studied dose dependency of the effects of verapamil on the absorption of Rho123. Because verapamil at 1 mM did not change the water absorption, it was considered that verapamil at 0.5 mM has no effect on water absorption either. The effect of 1 mM verapamil was similar to that of 0.5 mM, suggesting that the effect of verapamil is saturated at 0.5 mM or lower concentration in the jejunum. In contrast, in the ileum, there was no significant increase of Rho123 absorption in the presence of 0.5 mM verapamil compared with those in the absence of verapamil. These results suggested the different of sensitivity to verapamil between jejunum and ileum.

These regional differences may also be attributable to the pharmacological effects of verapamil other than inhibition of P-gp. For example, verapamil has been shown to increase intestinal motility both in the duodenum and jejunum, although a stronger effect was observed in the duodenum. When the intestinal motility is increased, it is expected to increase the intestinal absorption. Thus, the observed increase in Rho123 absorption in the presence of verapamil may be due not only to the inhibition of P-gp, but also to the increased absorption. These possibilities further suggest that it is necessary to consider the various effects of verapamil to examine the regional difference in the effect on P-gp in the whole body.

Because the log D value for verapamil at pH 7.4 is 2.7 or 4 to 5, verapamil has a similar or higher lipophilic property than Rho123. Furthermore, because the affinity of verapamil to P-gp is very high (Km = 30 \mu M), verapamil may be extruded by P-gp. Because of these mechanisms, verapamil inhibits P-gp by a competitive manner.

In the present experiment, the effect of verapamil was not apparent 30 min after the addition of verapamil with Rho123 in the ileum and colon. The reason for absence of the effect of verapamil may be a slower membrane transport of verapamil compared to that of Rho123. If this is the case, addition of verapamil before Rho123 was expected to show a stronger effect on Rho123 absorption. In fact, 60 min pretreatment with 0.5 mM verapamil showed a greater effect on Rho123 absorption than co-administration of 1 mM verapamil in the jejunum (p<0.05). The effect of pretreatment with 0.5 mM verapamil was also greater than that of co-administration of 0.5 mM of verapamil, although there was no statistical significance possibly because of the large deviation of the experimental values. In the ileum, 0.5 mM verapamil added simultaneously with Rho123 was not effective, whereas the pretreatment with verapamil increased the Rho123 absorption (p<0.05). In the jejunum, the decrease in Rho123 concentration in the loop was observed 30 min after the addition of verapamil together with Rho123, which was not observed in other regions of the intestine, suggesting the presence of some regional difference. These results suggest that preincubation with verapamil before the addition of Rho123 may effectively inhibit the P-gp function resulting in the increase in the Rho123 absorption.

In conclusion, the method we have developed is quite useful for evaluation of regional difference of net
absorption, as a sum of absorption and P-gp-mediated excretion. Using this method, it was demonstrated that there is regional difference in the P-gp-mediated excretion of Rho123 in the intestine and that the effect of P-gp is larger in jejunum and ileum than in colon. It was also confirmed that a modulation of P-gp by co-administration or pretreatment with P-gp inhibitor is significantly effective to improve P-gp substrate absorption from the intestine.

References


