Regular Article

Directional Transcellular Transport of Bisoprolol in P-glycoprotein-expressed LLC-GA5-COL150 Cells, but not in Renal Epithelial LLC-PK1 Cells

Katsutoshi TAHARA, Yuka KAGAWA, Mari TAKAAI, Masato TAGUCHI and Yukiya HASHIMOTO*

Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama, Japan

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Summary: To evaluate the mechanism responsible for the tubular secretion of bisoprolol, we compared transcellular transport of bisoprolol with that of tetraethylammonium (TEA), cimetidine, and quinidine across LLC-PK1 cell monolayers grown on porous membrane filters. TEA and cimetidine were actively transported in the basolateral-to-apical direction by the specific transport system. Pharmacokinetic analysis indicated that basolateral influx and apical efflux were cooperatively responsible for the directional transport of TEA and cimetidine. Lipophilic cationic drugs, quinidine, S-nicotine, and bisoprolol, significantly diminished basolateral influx and apical efflux clearance of cimetidine. However, transcellular transport of quinidine in the basolateral-to-apical direction was similar to that in the opposite direction in LLC-PK1 cells. In contrast, quinidine was transported actively in the basolateral-to-apical direction in P-glycoprotein-expressed LLC-GA5-COL150 cells. Pharmacokinetic analysis indicated that P-glycoprotein increased the apical efflux of quinidine and also decreased the apical influx of the drug. Basolateral-to-apical transport of bisoprolol was also similar to apical-to-basolateral transport in LLC-PK1 cells, whereas the drug was directionally transported from the basolateral to the apical side in LLC-GA5-COL150 cells. These results suggested that bisoprolol was not significantly transported via transport systems involved in the directional transport of TEA and cimetidine, but that P-glycoprotein was responsible for the directional transport of bisoprolol as well as quinidine in renal epithelial cells.

Keywords: bisoprolol; cationic drugs; renal secretion; transcellular transport; kinetic analysis; kidney epithelial cell line

Introduction

Bisoprolol is a selective β1-blocker without intrinsic sympathomimetic activity, and has been used widely in patients with cardiovascular diseases such as hypertension, angina pectoris, and cardiac arrhythmias in Japan. In addition, a large clinical trial (CIBIS-II) in Caucasians has shown a beneficial effect of bisoprolol on patients with chronic heart failure. Intestinal absorption of bisoprolol following oral administration is rapid, and the protein binding of bisoprolol in human plasma is approximately 30%. In healthy young subjects, 50% of the total dose of bisoprolol is metabolized in the liver, while 50% is excreted via the kidneys unchanged. We previously analyzed the pharmacokinetics of bisoprolol in middle-aged and elderly Japanese patients, and reported that the mean renal clearance value of bisoprolol was 15% higher than the creatinine clearance value. The finding suggested that not only glomerular filtration but also tubular secretion was responsible for renal elimination of the drug in humans as well as rats. The aim of this study was to evaluate the mechanism responsible for the tubular secretion of bisoprolol. The pig kidney epithelial cell line LLC-PK1 has been used to study the mechanisms of transcellular transport of cationic drugs and drug-drug interactions, whereas...
LLC-GA5-COL150 cells were established by transfection with human MDR1 cDNA to evaluate the involvement of P-glycoprotein on transcellular transport of drugs. To confirm the functional expression of the transport systems for cationic drugs in LLC-PK₁ and LLC-GA5-COL150 cells, we first performed pharmacokinetic analysis of the transcellular transport of radio-labeled tetraethylammonium (TEA), cimetidine and quinidine across cell monolayers grown on porous membrane filters. Then, we evaluated the transcellular transport of bisoprolol in LLC-PK₁ and LLC-GA5-COL150 cells.

Materials and Methods

Materials: 
- [14C]tetraethylammonium bromide (TEA) (2.04 GBq/mmol), [3H]quinidine (740 GBq/mmol), and [3H]mannitol (740 GBq/mmol) were purchased from American Radiolabeled Chemicals Inc. (St. Louis, MO, USA).
- [3H]cimetidine (900 MBq/mmol) was purchased from American Radiolabeled Chemicals Inc. (St. Louis, MO, USA).
- Bisoprolol hemifumarate was obtained from Moravek Biochemicals (Brea, CA, USA). Tetraethylammonium chloride and cimetidine were obtained from Nacalai Tesque Inc. (Kyoto, Japan). Quinidine hydrochloride monohydrate was purchased from Sigma (St. Louis, MO, USA).
- [14C]mannitol (740 GBq/mmol) was purchased from GE Healthcare (Little Chalfont, Buckinghamshire, UK).
- [3H]mannitol (1.96 GBq/mmol) was purchased from Moravek Biochemicals (Brea, CA, USA).

Cell culture and preparation of monolayers: 
LLC-PK₁ cells at passage 197 were obtained from the American Type Culture Collection (Manassas, VA, USA), and all experiments were carried out with the cells between passages 204 to 213. The cells were maintained by serial passage in plastic dishes with Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum (Valley Biochemical Inc., Winchester, VA, USA) in an atmosphere of 5% CO₂–95% air at 37°C. The medium was changed every second or third day, and when the cells reached 80–90% confluence, they were subcultured using a 0.02% EDTA/0.05% trypsin solution. LLC-PK₁ cells were seeded at a density of 5 × 10⁵ cells/cm² on a 1.12 cm² porous membrane (3 μm pore size) in a polyether membrane Transwell®-Clear insert (Costar, Cambridge, MA, USA) to evaluate the transcellular transport of cationic drugs. The seeded cells were maintained for 6 days to prepare differentiated cell monolayers. The maturity of the monolayer was judged by transepithelial electrical resistance (TEER). TEER was measured using a Millicell-ERS resistance system (Millipore, Bedford, MA, USA). LLC-PK₁ cell monolayers whose TEER was above 40 Ω·cm² were used to assess the transcellular transport of cationic drugs.

LLC-GA5-COL150 cells were obtained from the Riken Cell Bank (Tsukuba, Japan), and were cultured with medium supplemented with 150 ng/mL of colchicine for the stable expression of MDR1. LLC-GA5-COL150 cells were seeded at a density 7 × 10⁵ cells/cm² on a porous membrane. All culture media were replaced with medium without colchicine 1 day before transport experiments.

Estimation of cell volume of the cell monolayer: 
The volume of the cell monolayers was calculated from the amount of sulfanilamide that accumulated in the monolayer by simple diffusion under equilibrium conditions. Briefly, the cell monolayer was incubated for 60 min in 2 or 5 mg/mL sulfanilamide solution, and washed three times with ice-cold phosphate buffer, and the monolayer was collected for homogenization. The sulfanilamide concentration in the homogenized sample was spectrophotometrically determined at 550 nm after diazotization.

Transcellular transport of radio-labeled TEA, cimetidine, and quinidine: 
The transcellular transport of [14C]TEA, [3H]cimetidine, and [3H]quinidine in LLC-PK₁ cell monolayers prepared on a porous membrane was examined as described previously. In brief, the monolayer was pre-incubated for 1 hr at 37°C with culture medium (pH 8 or 6) containing an unlabeled drug to equilibrate the drug concentration (0.1–100 μM). After the equilibration period, the radio-labeled drug (0.25–2 μCi/well) was applied to the apical chamber (0.75 mL) to examine apical-to-basolateral transcellular transport. [3H]mannitol was used to estimate the paracellular transport and extracellular trapping of [14C]TEA, and [14C]mannitol was used to estimate those of [3H]cimetidine and [3H]quinidine. A volume (50 μL) of medium in the basolateral chamber (1.5 mL) was then collected after 1, 2, and 3 hr. Cells in the porous membrane were collected following the last collection of medium. Radioactivity in the medium and cells was determined using a liquid scintillation counter, and normalized against the initially applied doses. The time course of the transport of cationic drugs in the opposite (basolateral-to-apical) direction was examined in a similar manner. The drug concentration and medium pH in each experiment are shown in Table 1. Quinidine, S-nicotine, and bisoprolol were dissolved in medium to a final concentration of 100 μM, and the inhibitory effects of these cationic drugs on transcellular transport of cimetidine were examined in the same manner as described above. To investigate the contribution of P-glycoprotein to the transcellular transport of quinidine, another series of experiments was carried out using LLC-GA5-COL150 cells in the absence or presence of 500 μM bisoprolol.

Pharmacokinetic analysis of transcellular transport of radio-labeled drugs: 
The transcellular transport of TEA, cimetidine, and quinidine was analyzed in a model-dependent manner using NONMEM software running on a mainframe UNIX machine at the Kyoto University Data Processing Center. When transcellular transport of radio-labeled drugs was examined using LLC-PK₁ cell monolayers prepared on a porous membrane, the transcellular transport of cationic drugs was estimated as described above.

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drug transport is examined under the condition where the unlabeled drug concentration in the monolayer is equilibrated with that of the incubation medium in the apical and basolateral chambers, transport data for a small amount of a radio-labeled drug can be analyzed using a linear pharmacokinetic model.\(^{13-17}\) That is, the following mass balance equations were prepared for pharmacokinetic analysis:

\[
\frac{dX_A}{dt} = -\frac{CL_{A-C}}{V_A} \cdot X_A + \frac{CL_{C-A}}{V_C} \cdot X_C = \frac{CL_{A-B}}{V_A} \cdot X_A + \frac{CL_{B-A}}{V_B} \cdot X_B
\]  

(1)

\[
\frac{dX_B}{dt} = -\frac{CL_{B-C}}{V_B} \cdot X_B + \frac{CL_{C-B}}{V_C} \cdot X_C = -\frac{CL_{B-A}}{V_A} \cdot X_A - \frac{CL_{A-B}}{V_B} \cdot X_B
\]  

(2)

\[
\frac{dX_C}{dt} = \frac{CL_{A-C}}{V_A} \cdot X_A + \frac{CL_{B-C}}{V_B} \cdot X_B - \frac{CL_{C-A}}{V_C} \cdot X_C - \frac{CL_{C-B}}{V_C} \cdot X_C
\]  

(3)

where \(X_A, X_B,\) and \(X_C\) are the amounts of radio-labeled drugs in the apical chamber, basolateral chamber, and monolayer determined at time \(t\), respectively. \(V_A\) and \(V_B\) indicate the volume of the apical chamber (0.75 mL) and the basolateral chamber (1.5 mL), respectively. \(V_C\) indicates the cell volume of cell monolayers obtained from sulfanilamide accumulation experiments (1.12 \(\mu L/cm^2 \times 1.12 cm^2 = 1.25 \mu L\)). The influx and efflux clearance of radio-labeled drugs at the apical membrane of cells was designated as \(CL_{A-C}\) and \(CL_{C-A}\), respectively. The influx and efflux clearance of radio-labeled drugs at the basolateral membrane of cells was designated as \(CL_{B-C}\) and \(CL_{B-A}\), respectively. Paracellular transport clearance (\(CL_{A-B}\)) was estimated by analyzing the transport profile of radio-labeled mannitol using the following mass balance equations:

\[
\frac{dX_A}{dt} = -\frac{CL_{A-B}}{V_A} \cdot X_A - \frac{CL_{A-C}}{V_C} \cdot X_A
\]  

(4)

\[
\frac{dX_B}{dt} = -\frac{CL_{B-C}}{V_B} \cdot X_B - \frac{CL_{B-A}}{V_A} \cdot X_B
\]  

(5)

Transcellular transport of bisoprolol: Transcellular transport of bisoprolol in LLC-PK1 and LLC-GA5-COL150 cell monolayers prepared on a porous membrane was examined as described above with some modifications. In brief, the monolayer was pre-incubated for 1 hr at 37°C with culture medium (pH 6) in the absence or presence of 100 \(\mu M\) quinidine, and 10 \(\mu M\) bisoprolol medium was applied to the basolateral or apical side. A volume (50 \(\mu L\)) of medium on the opposite side was collected after 1, 2, and 3 hr. Bisoprolol concentration in the medium samples was determined by a reversed-phase HPLC method.\(^{3,5}\) A 50-\(\mu L\) aliquot of medium was alkalinized with 1.5 mL of glycine buffer (0.1 M, saturated with NaCl, pH 10.6), and mildly extracted with 5 mL of diethylether for 20 minutes. Bisoprolol was back-extracted from the organic phase with 0.4 mL of 0.05 N HCl for 20 min. A 50-\(\mu L\) aliquot of HCl solution was injected into an HPLC system. The column was COSMOSIL 5C18-AR-II (15 cm \(\times\) 4.6 mm; i.d. 4.5 \(\mu m\) particle size; Nacalai Tesque). The mobile phase consisted of 10 mM KH\(_2\)PO\(_4\) that contained 0.8% (w/v) triethanolamine adjusted to pH 3.3 with phosphoric acid and acetonitrile (80/20, v/v). The peaks were monitored at an excitation wavelength of 228 nm and an emission wavelength of 298 nm.\(^{3,5}\)

Statistical analysis: Values are expressed as the mean \(\pm\) S.E. in all figures, when error bars are not shown, they are smaller than the symbol. The statistical significance of the difference between mean values was calculated using a non-paired t-test. Multiple comparisons were performed using Scheffe’s test following one-way ANOVA. P values less than 0.05 were considered.

### Table 1. Influx and efflux clearance (\(\mu L/min/cm^2\)) of cationic drugs in LLC-PK1 cell monolayers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Conc. ((\mu M))</th>
<th>pH</th>
<th>(CL_{A-C})</th>
<th>(CL_{C-A})</th>
<th>(CL_{A-B})</th>
<th>(CL_{B-A})</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEA</td>
<td>100</td>
<td>8</td>
<td>0.682±0.046*</td>
<td>0.050±0.003*</td>
<td>0.012±0.001*</td>
<td>0.116±0.003*</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>6'</td>
<td>0.230±0.010</td>
<td>0.031±0.002</td>
<td>0.049±0.002</td>
<td>0.032±0.003</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>6</td>
<td>0.602±0.016*</td>
<td>0.030±0.002</td>
<td>0.226±0.005*</td>
<td>0.142±0.004*</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>3</td>
<td>6'</td>
<td>1.22±0.04</td>
<td>0.293±0.025</td>
<td>1.17±0.03</td>
<td>0.109±0.003</td>
</tr>
<tr>
<td>+ quinidine</td>
<td>3+100</td>
<td>6</td>
<td>0.25±0.03*</td>
<td>0.188±0.026*</td>
<td>0.26±0.02*</td>
<td>0.042±0.005*</td>
</tr>
<tr>
<td>+ bisoprol</td>
<td>3+100</td>
<td>6</td>
<td>0.69±0.05*</td>
<td>0.315±0.037</td>
<td>0.69±0.05*</td>
<td>0.045±0.006*</td>
</tr>
<tr>
<td>+ S-nicotine</td>
<td>3+100</td>
<td>6</td>
<td>0.82±0.04*</td>
<td>0.169±0.030</td>
<td>0.68±0.05*</td>
<td>0.100±0.016</td>
</tr>
<tr>
<td>Quinidine</td>
<td>100</td>
<td>8</td>
<td>4.40±0.32*</td>
<td>0.425±0.043</td>
<td>0.439±0.031</td>
<td>4.22±0.19*</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>6'</td>
<td>2.05±0.15</td>
<td>0.364±0.032</td>
<td>0.398±0.025</td>
<td>2.01±0.06</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>6</td>
<td>1.13±0.04*</td>
<td>0.136±0.008*</td>
<td>0.269±0.010*</td>
<td>1.53±0.06</td>
</tr>
<tr>
<td>Quinidine *</td>
<td>3</td>
<td>6'</td>
<td>1.33±0.05</td>
<td>0.155±0.008</td>
<td>0.363±0.043</td>
<td>0.55±0.06</td>
</tr>
<tr>
<td>+ bisoprol</td>
<td>3+500</td>
<td>6</td>
<td>1.48±0.05</td>
<td>0.210±0.010*</td>
<td>0.565±0.020</td>
<td>1.12±0.04*</td>
</tr>
</tbody>
</table>

Values are expressed as the mean \(\pm\) S.E. for 5–10 experiments. \(CL_{A-C}\) and \(CL_{C-A}\) represent the influx and efflux clearance at the apical membrane, respectively. \(CL_{A-B}\) and \(CL_{B-A}\) represent the influx and efflux clearance at the basolateral membrane, respectively. \(CL_{A-B}\) represents the paracellular transport clearance. *Control condition, °Experiments using LLC-GA5-COL150 cell monolayers, *\(p<0.05\) as compared with each control.

\[\frac{dX_B}{dt} = \frac{CL_{A-B}}{V_A} \cdot X_A - \frac{CL_{A-B}}{V_B} \cdot X_B\]
Transcellular Transport of Bisoprolol in LLC-PK₁

Results and Discussion

Transcellular transport and membrane transport clearance of TEA: We first analyzed the transcellular transport of TEA as a prototypical substrate for organic cation transport systems in LLC-PK₁ cell monolayers. TEA was transported directionally from the basolateral side to the apical side at medium pH 6, but not at pH 8, and cellular accumulation of TEA at pH 6 was significantly decreased as compared with at pH 8 (Fig. 1A and 1B). The estimated basolateral influx (CL_B→C) and efflux (CL_C→B) clearance values of 100 μM TEA were lower at pH 6 than at pH 8 (Table 1). On the other hand, when the medium pH was decreased from 8 to 6, the apical influx clearance (CL_A→C) value of 100 μM TEA decreased, whereas the apical efflux clearance (CL_C→A) value increased markedly. When the unlabeled drug concentration of TEA was decreased from 100 μM to 10 μM, the fraction of apical-to-basolateral transport of the drug was unaffected, whereas the fraction of basolateral-to-apical transport was increased markedly (Fig. 1C). CL_B→C, CL_A→C, and CL_C→A values at pH 6 were increased significantly at 10 μM as compared with 100 μM (Table 1). The increases in CL_B→C and CL_C→A values seemed to be mainly responsible for the increase in basolateral-to-apical transport of TEA at a concentration of 10 μM. These results confirmed that TEA was transported by high-affinity transport systems at both basolateral and apical membranes in LLC-PK₁ cells.

LLC-PK₁ cell monolayers grown on porous membrane filters express organic cation transporters in both basolateral and apical membranes.30 LLC-PK₁ cells express the proton/organic cation antipporter on the apical membrane, and apical efflux of TEA was markedly stimulated by acidification of the apical medium.4,5 On the other hand, the transport system involved in basolateral uptake of TEA in LLC-PK₁ cells is dependent on the inside negative potential, and basolateral uptake of the drug was decreased by lowering basolateral medium pH.18,19 The membrane transport characteristics of TEA in LLC-PK₁ cells in the present study are consistent with the previous findings.

Transcellular transport and membrane transport clearance of cimetidine: Cimetidine may share a common transport system with TEA in basolateral and brush-border membranes in renal epithelial cells.20 Tritium-labeled cimetidine is commercially available, and can be used for the transport experiment at lower unlabeled drug concentrations, as compared with carbon-14-labeled TEA. To further evaluate the cation transport systems in LLC-PK₁ cells, we next analyzed the transcellular transport of cimetidine across cell monolayers at the therapeutic drug concentration of 3 μM. Cimetidine was transported directionally from the basolateral side to the apical side (Fig. 2A), and the mean CL_B→C and CL_C→A values of cimetidine were much greater than the other clearance values of the drug (Table 1). In addition, CL_B→C and CL_C→A values of cimetidine at a concentration of 3 μM were much larger than those of TEA at a concentration of 10 μM (Table 1).

To evaluate the inhibitory effect of lipophilic cationic drugs on transport systems for organic cations, we analyzed the transcellular transport of cimetidine in the presence of 100 μM quinidine, bisoprolol, and S-nicotine in LLC-PK₁ cells. Quinidine inhibited the basolateral-to-apical transport of cimetidine more significantly than bisoprolol and S-nicotine (Fig. 2B-D). In addition, quinidine diminished the CL_B→C and CL_C→A values of cimetidine more potently than bisoprolol and S-nicotine (Table 1). Our present results seemed to be consistent with the hypothesis presented by Ullrich and co-workers.21 That is, they reported that the inhibitory effect of cationic drugs on renal basolateral and brush-border organic cation transport increased with increasing lipophilicity of drugs.21 In addition, the logP values of quinidine, bi-
Fig. 2. Transcellular transport and accumulation of cimetidine in LLC-PK₁ cell monolayers
A: 3 μM cimetidine alone at pH 6, B: + 100 μM quinidine, C: + 100 μM bisoprolol, D: + 100 μM S-nicotine. Symbols and curves are the same as in Fig. 1. Data are expressed as the mean ± S.E. of 6–8 experiments.

Fig. 3. Transcellular transport and accumulation of quinidine in the LLC-PK₁ (A, B, C) and LLC-GA5-COL150 (D, E) cell monolayers
A: 100 μM at pH 8, B: 100 μM at pH 6, C: 0.1 μM at pH 6, D: 3 μM at pH 6, E: 3 μM quinidine + 500 μM bisoprolol at pH 6. Symbols and curves are the same as in Fig. 1. Data are expressed as the mean ± S.E. of 8–10 experiments.
soprolol, and S-nicotine were reported to be 3.44, 1.87, and 1.17, respectively.22)

Transcellular transport and membrane transport clearance of quinidine in LLC-PK₁ and LLC-GA5-COL150 cells: We analyzed the transcellular transport of quinidine across LLC-PK₁ cell monolayers (Fig. 3A–C). Transcellular transport of quinidine in the basolateral-to-apical direction at a concentration of 100 µM was not different from that in the opposite direction at medium pH 8 and 6 (Fig. 3A and B). CL_{b→a} and CL_{A→B} values of quinidine at pH 6 were lower than those at pH 8 (Table 1), which was consistent with the results that cellular accumulation of the drug was decreased at pH 6 as compared with pH 8 (Fig. 3A and B). On the other hand, the transport fraction of quinidine at a concentration of 0.1 µM was lower than that at a concentration of 100 µM (Fig. 3C), and membrane clearance values of quinidine at 0.1 µM tended to be less than those at 100 µM (Table 1). These results suggested that quinidine is not significantly transported via transport systems involved in the directional transport of TEA and cimetidine in LLC-PK₁ cells. In addition, the passive diffusion of quinidine may be decreased with the decrease in the unionized fraction at medium pH 6 or in the unbound fraction at a drug concentration of 0.1 µM.

We then evaluated the involvement of P-glycoprotein in the transepithelial transport of quinidine using LLC-GA5-COL150 cells. Quinidine was transported directionally from the basolateral side to the apical side in LLC-GA5-COL150 cells (Fig. 3D). The CL_{c→a} value was greater in LLC-GA5-COL150 cells than in LLC-PK₁ cells (Table 1). In contrast, the CL_{A→B} value was much smaller in LLC-GA5-COL150 cells than in LLC-PK₁ cells. When bisoprolol was added to the medium, basolateral-to-apical transport of quinidine was unaffected, whereas apical-to-basolateral transport was increased (Fig. 3E). The CL_{c→a} value of quinidine was not altered by the presence of bisoprolol, whereas the CL_{A→B} value was significantly increased by bisoprolol (Table 1). These results suggested that the decrease in apical influx of quinidine was mainly responsible for directional transport of the drug in LLC-GA5-COL150 cells.

LLC-PK₁ cells express a marginal level of endogenous P-glycoprotein, whereas LLC-GA5-COL150 cells overexpress P-glycoprotein on the apical membrane.29) The molecular model suggested that specific recognition of the substrate by P-glycoprotein occurs at the membrane surface, and that ATP-energized protein forms a gated pore-like structure, allowing the movement of substrates through the membrane.29) On the other hand, since the substrates of P-glycoprotein are distributed into lipid bilayers, it has been suggested that drug extrusion by P-glycoprotein may occur directly from the lipid phase of the plasma membrane without the actual appearance of the drug in the cytoplasm.29) The latter hypothesis seems to be in accord with the transport characteristics of quinidine in LLC-GA5-COL150 cells, and may partly explain the moderate effect of high concentration of bisoprolol on the transcellular transport and cellular accumulation of quinidine (Fig. 3D and E).

Transcellular transport of bisoprolol in LLC-PK₁ and LLC-GA5-COL150 cells: We finally evaluated the transcellular transport of bisoprolol in LLC-PK₁ and LLC-GA5-COL150 cells (Fig. 4). Transcellular transport of bisoprolol in the basolateral-to-apical direction in LLC-PK₁ cells was similar to that in the opposite direction at a concentration of 10 µM (Fig. 4A). Addition of quinidine did not significantly affect transcellular transport of bisoprolol in both directions in LLC-PK₁ cells (Fig. 4A). These findings suggested that bisoprolol was not significantly transported by transport systems involved in the transport of TEA and cimetidine in LLC-PK₁ cells. On the other hand, bisoprolol was transported directionally from the basolateral side to the apical side in LLC-GA5-COL150 cells (Fig. 4B). That is, basolateral-to-apical transport of bisoprolol in LLC-GA5-COL150 cells increased slightly as compared with in LLC-PK₁ cells, whereas apical-to-basolateral transport decreased markedly. Addition of quinidine to the medium decreased basolateral-to-apical transport of bisoprolol, and increased apical-to-basolateral transport (Fig. 4B). These findings suggested that bisoprolol as well as quinidine was actively transported by P-glycoprotein in LLC-GA5-COL150 cells.

Conclusion

Bisoprolol was not transported via transport systems
involved in the TEA and cimetidine transport in renal epithelial LLC-PK₁ cells. On the other hand, bisoprolol as well as quinidine was transported directionally from the basolateral side to the apical side in P-glycoprotein-expressed LLC-GA5-COL150 cells. The present findings may provide useful information on mechanisms responsible for renal tubular secretion of bisoprolol.

References


