Carrier-Mediated Lung Distribution of HSR-903, a New Quinolone Antibacterial Agent

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ABSTRACT

HSR-903 (S)-(-)-5-amino-7-(7-amino-5-azaaspiro[2.4]hept-5-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid methanesulfonate) is a newly synthesized quinolone with a potent antibacterial activity and a low toxicity. The lung concentration of unchanged HSR-903 was about nine times higher than that in plasma after oral administration (5 mg/kg) in rats. In comparative studies, HSR-903 was accumulated more efficiently than levofloxacin, ciprofloxacin, and lomefloxacin in rat lung. To clarify the mechanism of the specific distribution of HSR-903 into the lung, the uptake of [14C]HSR-903 was studied using isolated rat lung cells and an isolated rat lung perfusion technique. Initial uptake of HSR-903 by isolated lung cells was temperature dependent, saturable, stereospecific, and Na\(^+\) and Cl\(^-\) dependent. The Hill coefficients (1.90 for Na\(^+\) and 1.13 for Cl\(^-\)) suggest that two Na\(^+\) and one Cl\(^-\) are associated with the transport of one HSR-903 molecule. The uptake of HSR-903 was inhibited by other quinolone antibacterial agents, grepafloxacin, and sparfloxacin. The extraction ratio of HSR-903 in isolated lung perfusion was temperature dependent and saturable. These findings suggest that HSR-903 is taken up by the lung cells via a carrier-mediated transport mechanism, resulting in a concentration distribution into the lung.

Materials and Methods

Chemicals. HSR-903, [14C]HSR-903 (specific activity, 256 kBq/mg base, Fig. 1), and other quinolone derivatives were synthesized by Hokuriku Seiyaku Co., Ltd. (Fukui, Japan). [3H]Inulin was purchased from Amersham Co. (Tokyo, Japan). Protease type VIII and rotenone were purchased from Sigma Chemical Co. (St. Louis, MO). All other reagents were commercially available and of reagent grade.

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ABBREVIATIONS: \(V_d\), distribution volume; KHB, Krebs-Henseleit buffer; \(J_i\), initial uptake rate; \(s\), a concentration of the substrate; \(K_m\), apparent Michaelis constant; \(u_{max}\), maximal uptake rate; \(k_d\), nonsaturable uptake clearance; AUC, area under the concentration curve.
adherent volume determined by the uptake of [3H]inulin was less than 90% uptake, a mixture of [14C]HSR-903 (10 \mu M) were corrected for the nonspecific uptake of [3H]inulin. Because the nonspecific uptake was hardly affected on the uptake of HSR-903. The initial uptake rate increased until 15 s.

Preparation of Isolated Lung Cells. Isolated lung cells from rats were prepared using a minor modification of the method of Dawson et al. (1982) and Kohno et al. (1990). Briefly, rats were anesthetized with a 10 mg/kg i.v. dose of sodium pentobarbital, the pulmonary artery was cannulated, and the lung was perfused with Krebs-Henseleit buffer (KHB, pH 7.4) containing 2.5% BSA and 5 mM glucose. The trachea was then cannulated and perfused for 20 min with Ca\(^{2+}\)-, Mg\(^{2+}\)-free Hank’s buffer (pH 7.4) containing 0.1% protease type VIII and 1 mM EDTA. The lung was then minced, and the lung cells were purified by centrifugation at 4°C and 80g for 5 min. The resultant pellets were suspended in KHB and used at a concentration of 1 × 10^7 cells/0.2 ml. When sodium or chloride ions were replaced with other cations or anions, the obtained cell pellets were suspended in sodium- or chloride-free buffer, respectively. The composition of sodium-free buffer was the same with KHB, except that the sodium chloride was replaced isotonically with potassium bicarbonate. Similarly, for chloride-free buffer, sodium chloride was replaced with sodium gluconate, sodium nitrate, or sodium sulfate, and potassium chloride was replaced with potassium gluconate, potassium nitrate, or potassium sulfate.

Uptake Study. Drug uptake was initiated by adding the test compound to the preincubated (37°C for 5 min) cell suspension (10^7 cells/0.2 ml). At a designated time, the reaction was terminated by separating the cells from the medium by means of a centrifugal filtration technique (Schwarz et al., 1977). The concentration of [14C]HSR-903 was 10 \mu M except for the concentration-dependence study. The lower layer of the cell pellet was neutralized with 0.1 N HCl, the resultant cell pellet or 100 \mu l of supernatant were mixed well with scintillation cocktail, Cleasol (Nacalai Tesque, Kyoto, Japan), and then the radioactivity was determined. The uptake rates of HSR-903 were corrected for the adherent medium volume evaluated from the apparent uptake of [3H]Hinulin. Because the nonspecific adherent volume determined by the uptake of [3H]Hinulin was less than 10% of apparent uptake of HSR-903, it is thought that the value hardly affected on the uptake of HSR-903. The initial uptake rate was evaluated from the uptake at 15 s, as uptake was linearly increased until 15 s.

Animals. Male Sprague-Dawley rats (210–260 g) were purchased from Charles River Japan Inc. (Kanagawa, Japan) and were allowed free access to laboratory chow and water.

In Vivo Study. The study was performed according to the Guidelines for the Care and Use of Laboratory Animals in Takara-machi Campus of Kanazawa University and was approved by the Committee of Ethics of Animal Experimentation of Kanazawa University, Takara-machi Campus.

Lung and plasma concentrations of unchanged quinolones were determined after single oral administration of HSR-903, ciprofloxacin, lomefloxacin, or levofloxacin at a dose of 5 mg/kg. At 15, 30, 60, 120, and 240 min after dosing, the rats under ether anesthesia were sacrificed by exsanguination from the abdominal aorta and dissected immediately. The concentrations of unchanged quinolones in lung and plasma were determined.

Isolated Lung Perfusion Study. Isolated lung was prepared according to the method of Camus et al. (1990). Briefly, rats were anesthetized with a 50 mg/kg i.p. dose of sodium pentobarbital, tracheostomized, and ventilated (5% CO\(_2\) in O\(_2\)) via a tracheal cannula on an animal ventilator (Harvard Apparatus, South Natick, MA) at 60 Hz with 2- to 3-ml tidal volume. Heparin (1000 I.U./kg) was injected into the femoral vein, and the lungs were surgically removed. The pulmonary artery was perfused with Krebs-Ringer-bicarbonate buffer solution (pH 7.4) supplemented with 4.5% BSA (Fraction V, Sigma). In this solution, HSR-903 showed 30% protein binding.

After a 10-min perfusion with drug-free medium for equilibration, the perfusion medium was changed to the medium containing a known concentration of HSR-903 (10 \mu M [14C]HSR-903) and [3H]Hinulin (37 kBq/ml), and single-pass perfusion through the lung was conducted for 20 min. The effluent was collected into plastic tubes every 2 min. The extraction ratio was obtained by dividing the difference of concentration between the inflow medium and outflow medium by the concentration of inflow medium.

Analytical Method. The concentrations of unchanged HSR-903 were determined by HPLC assay. Briefly, samples of accurately weighed tissue (0.1 g) were homogenized (Polytron, Kinematica, Switzerland) with 0.1 ml of 1/15 M phosphate buffer (pH 7.0), and samples of plasma (0.1 ml) were well mixed with 0.1 ml of the same buffer. Each sample was mixed well with 0.1 ml of 1 N NaOH and 3 ml of diethyl ether, then centrifuged at 3000 rpm for 5 min. The resultant aqueous layer was vigorously shaken with 0.5 ml of 1 M phosphate buffer (pH 7.0) and 6 ml of chloroform-isooamyl alcohol mixture (95:5, v/v) for 10 min. After centrifugation of the mixture at 3000 rpm for 10 min, a 5-ml aliquot of the organic layer was put into a glass tube and evaporated to dryness at 37°C under reduced pressure. The residue was dissolved in 0.5 ml of 0.1 M citrate buffer (pH 4.0)-acetoniitrile (3:1, v/v), and an aliquot was subjected to HPLC [model BIP-I solvent delivery system (Japan Spectroscopic Co., Tokyo, Japan), UVIDEC-100-V UV detector (Japan Spectroscopic Co.), 4.6 mm × 15 cm TSKgel ODS-80TM analytical column (5-µm particle size; Tosoh, Tokyo, Japan)]. The mobile phase was composed of 0.03 M ammonium phosphate buffer (pH 2.5)-acetoniitrile (3:1, v/v). The flow rate was 1.2 ml/min and the eluate was monitored at 308 nm. Data analysis was done with a Chromatopac C-R7A (Shimadzu Corp., Kyoto, Japan). In these conditions, HSR-903 eluted as a well-defined peak without any interference of contaminants in lung cell.

The concentrations of unchanged levofloxacin, ciprofloxacin, and lomefloxacin in lung and plasma after oral administration were determined by bioassay using thin-layer cup with Escherichia coli kp as an indicator organism. The sample preparation was performed according to the method of Yoshizumi et al. (1998).

In both HPLC and bioassay, the limits of quantitation was 0.05 \mu g/ml or \mu g/g tissue, the coefficients of variation were within 10% for all quinolones, and the recovery from lung tissue was about 50% for HSR-903 and almost complete for other quinolones.

The radioactivity was determined with an LSC-1000 liquid scintillation counter (Alola, Co., Tokyo, Japan). The cellular ATP content of a perchloric acid extract of lung cells was measured by the luciferin-luciferase procedure (Duluca and McElloy, 1978) using an assay kit (Analytical Luminescence Laboratory Inc., San Diego, CA).

Data Analysis. Kinetic parameters (Kd, Jmax, and kdc) of concentration-dependent uptake were estimated according to the following equation (eq. 1):

\[
j = \frac{J_{\text{max}} \times s}{(K_i + s)} + k_d \times s
\]

where \(j\) is the initial uptake rate of the drug (nmol/15 s/10^7 cells), \(s\) is a concentration of the substrate (\mu M), \(K_i\) is the apparent Michaelis constant (\mu M), \(J_{\text{max}}\) is the maximal uptake rate (nmol/15 s/10^7 cells), and \(k_d\) is the dissociation constant.

Fig. 1. Chemical structure of [14C]HSR-903. *Shows labeled position.
and \( k_d \) represents the nonsaturable uptake clearance (\( \mu l/15 \ s/10^7 \) cells). Hill analysis parameters (\( K_t' \), \( J_{\text{max}} \), and \( n \)) were estimated according to the following equation (eq. 2):

\[
\frac{J}{J_{\text{max}}} = \frac{J_{\text{max}} \times s^n}{(K_t' + s^n)}
\]

Where \( K_t' \) is the apparent Michaelis constant (\( \mu M \)), \( J_{\text{max}} \) is the maximal uptake rate (nmol/s/10^7 cells), and \( n \) is the Hill coefficient. The above equations were fitted to the uptake data sets by an iterative nonlinear least-squares analysis using the MULTI program (Yamaoka et al., 1981) to obtain the best estimates of the kinetic parameters.

ANOVA was used to compare the means between groups.

Results

Pharmacokinetic Study of HSR-903. After 5 mg/kg oral administration of HSR-903 or other quinolones in rats, the absorption of the drugs was rapid, resulting in the first sample taken at 0.25 h having the highest concentration. Subsequently, the concentration declined rapidly (Fig. 2). Because HSR-903 is expected to be used for the treatment of pulmonary infections, the lung concentration of unchanged drug was determined after 5 mg/kg oral administration to rats and was compared with those of other quinolones (Fig. 2). The unchanged HSR-903 concentration in the lung was significantly higher than that in plasma. Furthermore, the lung-to-plasma concentration ratio of HSR-903 (12.7 ± 0.8, at 4 h; mean ± S.E., \( n = 5 \)) was much higher than those of levofloxacin (1.3 ± 0.1, \( n = 5 \)), ciprofloxacin (0.8 ± 0.2, \( n = 5 \)), and lomefloxacin (0.9 ± 0.0, \( n = 5 \)). The area under the concentration curve (AUC_{lung} / AUC_{plasma}) ratio until 4 h was 11.0 for HSR-903, 1.1 for lomefloxacin, 0.6 for levofloxacin, and 1.6 for ciprofloxacin.

Time Course of HSR-903 Uptake by Isolated Lung Cells. Figure 3 shows the time course of the uptake of [\(^{14}C\)]HSR-903 into isolated lung cells. The uptake of [\(^{14}C\)]HSR-903 at 37°C increased linearly up to 15 s. The uptake of [\(^{14}C\)]HSR-903 at 5 min was 0.32 nmol/10^7 cells, representing a 33-fold accumulation against the concentration gradient when calculated with the cell volume of 0.97 \( \mu l/10^7 \) cells obtained in the present study. Moreover, the uptake showed a marked temperature dependence (Fig. 3).

Stereospecificity and Concentration Dependence of HSR-903 Uptake by Isolated Lung Cells. To determine the stereospecificity of the lung uptake of HSR-903, uptake of [\(^{14}C\)]HSR-903 was determined in the presence of various concentrations of unlabeled HSR-903 (S-isomer) and its stereoisomer (R-isomer). As shown in Table 1 and Fig. 4, the S- and R-isomers both exhibited saturable uptake with different kinetic parameters as follows: S-isomer, \( K_t = 33.6 \mu M, J_{\text{max}} = 0.250 \text{ nmol/15 s/10}^7 \text{ cells} \) and \( k_d = 1.12 \mu l/10^7 \text{ cells/15 s} \); R-isomer, \( K_t = 59.2 \mu M, J_{\text{max}} = 0.205 \text{ nmol/15 s/10}^7 \text{ cells} \) and \( k_d = 1.00 \mu l/10^7 \text{ cells/15 s} \). In terms of \( J_{\text{max}} / K_t, \) S-isomer, was more efficiently transported than its R-isomer (\( J_{\text{max}} / K_t \) of 7.45 and 3.45 \( \mu l/10^7 \text{ cells/15 s} \), respectively).

Effect of Ionic Composition of Medium on HSR-903 Uptake by Isolated Lung Cells. The uptake of [\(^{14}C\)]HSR-903 was significantly reduced by substitution of choline, potassium, or lithium for sodium (Table 2). Similarly, the uptake was significantly reduced by substitution of nitrate, sulfonate, or gluconate for chloride (Table 2). Figure 5 shows...
the relationship between the uptake of $[^{14}\text{C}]$HSR-903 and the concentration of sodium or chloride ion. The Hill coefficients of sodium and chloride ions were 1.90 and 1.13, respectively. To clarify the nature of the sodium requirement in HSR-903 uptake, the time course of uptake of $[^{14}\text{C}]$HSR-903 in the presence and absence of a sodium gradient was examined by using ATP-depleted cells. The cellular ATP content was reduced by earlier incubation with rotenone (30 μM) for 5 min, being decreased from 7.69 nmol/107 cells in normal cells to 2 nmol/107 cells in rotenone-treated cells. As shown in Fig. 6, the uptake exhibited a marked overshoot phenomenon only in the presence of an Na⁺ gradient.

### Inhibition by Quinolones of HSR-903 Uptake by Isolated Lung Cells

To determine the structural specificity of the lung uptake of HSR-903, the effect of other quinolone antibacterial agents on $[^{14}\text{C}]$HSR-903 uptake was examined. Unlabeled HSR-903, grepafloxacin, and sparfloxacin reduced the uptake of $[^{14}\text{C}]$HSR-903, whereas other quinolone antibacterial agents were not significantly inhibitory (Table 3).

### Lung Perfusion Study

To confirm the existence of a specific transport system for HSR-903 in the intact lung, the extraction ratio in the steady state was investigated by the isolated rat lung perfusion technique. Because preliminary experiments showed that the extraction ratio reached a steady state at about 6 min, the extraction of HSR-903 was measured between 6 and 14 min (Fig. 7). HSR-903 (50 μM) reduced the extraction ratio by 30 to 40%, and 500 μM produced a significant decrease in the extraction ratio by 60 to 70% at 37°C. Furthermore, the extraction ratio of HSR-903 decreased by 60 to 70% at 4°C. On the other hand, the extraction ratio of $[^{3}\text{H}]$inulin, which is distributed only in the extracellular space, did not change in the presence of a high concentration of HSR-903 (500 μM) or at 4°C.

### Discussion

New quinolone antibacterial agents such as sparfloxacin are well distributed to many tissues (Nakamura et al., 1990; Matsunaga et al., 1991). However, in the case of HSR-903, a newly synthesized quinolone antibacterial agent, a particularly high concentration of unchanged drug was observed in the lung. Indeed, HSR-903 was accumulated in the lung, exhibiting a lung-to-plasma concentration ratio at 4 h and AUClung to AUCplasma ratio until 4 h of about 12.7 and 11, respectively, whereas other quinolones gave significantly small values close to unity. Similar high lung distribution of HSR-903 compared with sparfloxacin and levofloxacin was reported in mice (Yoshizumi et al., 1998). Moreover, the plasma-free fraction in rats were reported to be 0.45 for HSR-903 (M. Murata, E. Takahara, O. Nagata, H. Kato, I. Tamai, and A. Tsuji, submitted for publication), 0.28 for levofloxacin (Okezaki et al., 1988), 0.40 to 0.51 for levofloxacin (Aoki et al., 1991), and 0.33 for ciprofloxacin (Siefert et al., 1986). Accordingly, when considering these protein binding values, lung-to-plasma unbound concentration ratio of HSR-903 will be about 5-fold larger than other quinolones, suggesting that lung distribution of HSR-903 is efficient. These data suggest that HSR-903 is more efficiently accumulated in lung tissue in vivo than ciprofloxacin, levofloxacin, or levofloxacin. These results prompted us to examine the mechanisms involved in the lung distribution.

For that purpose, isolated rat lung cells were used. As shown in Fig. 2, the plasma $C_{\text{max}}$ of HSR-903 was 1 μg/ml, and the pharmacological concentration was reported to be about 2 μg/ml (Takahashi et al., 1997). We used the in vitro drug concentration of 10 μM, approximately 5 μg/ml as total concentration, because it was minimum concentration to allow quantitatively reliable experiments by the low specific activity of radiolabeled compound. The steady-state uptake of $[^{14}\text{C}]$HSR-903 at 5 min corresponded to a 33-fold accumulation against the concentration gradient. Moreover, the uptake showed marked temperature dependence (Fig. 3).

Stereospecificity is also good evidence for the participation of a carrier-mediated transport mechanism. A kinetic study of the inhibitory effect showed that the initial uptakes of both HSR-903 (S-isomer) and its R-isomer were saturable and that S-isomer was 2.2 times more efficiently transported, in terms of $J_{\text{max}}/K_t$. These results suggest that HSR-903 was taken up by lung cells in a stereospecific manner. Because the therapeutic plasma concentration (about 1–2 μM) was significantly lower than the $K_t$ value obtained in the present study, the saturable transport of HSR-903 was evaluated as $J_{\text{max}}/K_t$, which was calculated to be 7.45 μl/107 cells/15 s. The ratio between $J_{\text{max}}/K_t$ value and $k_1$ (1.12 μl/107 cells/15 s) obtained in the present study was about 7.1 at therapeutic concentration. The lung uptake of HSR-903 can be mainly accounted for by this saturable transport.

The effects of the replacement of Na⁺ by choline⁺, K⁺, and Li⁺ and of Cl⁻ by NO₃⁻, SO₄²⁻, and gluconate⁻ on the $[^{14}\text{C}]$HSR-903 uptake (Table 2) indicate that the uptake is Na⁺ and Cl⁻ dependent. The Hill coefficients (1.90 for Na⁺ and 1.13 for Cl⁻) suggest that two Na⁺ and one Cl⁻ are associated with the transport of one HSR-903 molecule. To clarify the nature of the sodium requirement in HSR-903 uptake, the time course of uptake of $[^{14}\text{C}]$HSR-903 in the presence and absence of a sodium gradient was examined by using ATP-depleted cells in which the ATP content was reduced to 26% of the control by the treatment of rotenone (30 μM). The uptake of HSR-903 exhibited a marked overshoot phenomenon in the presence of sodium gradient. Because a sodium gradient cannot be maintained well in the ATP-depleted cells and dissipates with time, apparent transient uphill uptake suggests that sodium gradient works as the driving force for the transport of HSR-903. This observation cannot be explained by the binding of HSR-903 to the cell component. Accordingly, the concentrative HSR-903 uptake is suggested to be driven by the sodium gradient, but not by the binding to the cells.

Okumura et al. (1978, 1989) and Yoshida et al. (1987, 1989) reported that common binding sites for basic drugs exist in lung tissues, and that the affinity of these sites is dependent

### Table 1: Inhibitory effect on $[^{14}\text{C}]$HSR-903 (10 μM) uptake by unlabeled HSR-903 (S-isomer) and its R-isomer

<table>
<thead>
<tr>
<th>Inhibitor concentration</th>
<th>Uptakea</th>
</tr>
</thead>
<tbody>
<tr>
<td>μM</td>
<td>pmol/10⁷ cells</td>
</tr>
<tr>
<td>Control</td>
<td>20.26 ± 1.44</td>
</tr>
<tr>
<td>HSR-903 (S-isomer)</td>
<td>15.23 ± 0.72</td>
</tr>
<tr>
<td>500</td>
<td>10.49 ± 0.79</td>
</tr>
<tr>
<td>R-isomer</td>
<td>17.68 ± 0.85</td>
</tr>
<tr>
<td>500</td>
<td>11.45 ± 1.31</td>
</tr>
</tbody>
</table>

Each value indicates mean ± S.E. from four experiments.

a Uptake was determined at 15 s.

b $P < .05$.

c $P < .01$, by ANOVA.
on the lipid solubility of basic drugs. Partition coefficients of HSR-903, grepafloxacin, and sparfloxacin measured in an octanol-So¨rensen buffer (pH 7.4) system at 37°C were 2.58, 5.91, and 1.14, respectively, and these values are greater than those of other quinolone antibacterial agents used in this study (0.6). Moreover, unlabeled HSR-903 and grepafloxacin caused large reductions and sparfloxacin also reduced the uptake of [14C]HSR-903, whereas other quinolone antibacterial agents were not inhibitory (Table 3). These findings indicate that several quinolone antibacterial agents, including HSR-903, are taken up into lung cells by a common transport system, and lipophilicity may contribute in part to the affinity for the transporter.

To correlate the suggested transport mechanism with the in vivo lung distribution, the isolated lung perfusion method was used. The steady-state extraction ratio of [3H]inulin, which distributes only in the extracellular space, was not changed in the presence of HSR-903 or at 4°C. This result suggests that the lung was not damaged in the present study. Although extraction of HSR-903 was apparently not so high when compared with that from in vitro isolated lung cell study, the extraction ratio of HSR-903 decreased markedly at

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>% of control</th>
</tr>
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<tbody>
<tr>
<td>HSR-903</td>
<td>51.71 ± 3.78a</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>58.91 ± 4.21a</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>77.01 ± 3.73b</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>79.53 ± 5.31</td>
</tr>
<tr>
<td>Fleroxacin</td>
<td>89.85 ± 9.42</td>
</tr>
<tr>
<td>Tosufloxacin</td>
<td>117.97 ± 4.34</td>
</tr>
<tr>
<td>Lomefloxacin</td>
<td>99.23 ± 6.03</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>88.35 ± 9.81</td>
</tr>
<tr>
<td>Enoxacin</td>
<td>84.91 ± 6.17</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>90.81 ± 5.14</td>
</tr>
</tbody>
</table>

Each value indicates mean ± S.E. from four experiments.  

Fig. 5. Time course of [14C]HSR-903 (10 μM) uptake in the presence (●) and absence (○) of an Na+ gradient by ATP-depleted lung cells. Each symbol and vertical bar represents mean and S.E. from five to eight experiments, respectively.

TABLE 3
Inhibition of [14C]HSR-903 (10 μM) uptake by various quinolones (500 μM)

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSR-903</td>
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</tbody>
</table>

Each value indicates mean ± S.E. from four experiments.  

a P < .01.  
b P < .05, by ANOVA.
4°C and in the presence of unlabeled HSR-903 in a concentration-dependent manner, which is consistent with results obtained from in vitro study. Accordingly, we concluded that HSR-903 was taken up by the lung via a carrier-mediated transport mechanism in vivo. Apparently, lower extraction of HSR-903 in lung perfusion study than that expected from in vivo lung distribution (Fig. 2) may be ascribed to the decreased viability of the tissues by isolating from normal blood supply.

Iwasawa and Gillis (1974) and Cross et al. (1974) reported that 5-hydroxytryptamine and 1-norepinephrine were taken up into the lung by Na\(^+\)-dependent active transport, and the site of uptake in the lung was the endothelial cells of the vasculature. Gordonsmith et al. (1985) and Wyatt et al. (1988) reported that endogenous oligoamines (putrescine, spermidine, and spermine) were taken up into alveolar type I and type II cells by Na\(^+\)-independent active transport. However, \(^{[14]}\)C HSR-903 was not affected by 10 mM 5-hydroxytryptamine or putrescine (data not shown). More studies will be needed to characterize the HSR-903 transporter.

We conclude that HSR-903 is accumulated in the rat lung by an Na\(^+\)- and Cl\(^-\)-dependent carrier-mediated transport mechanism. Moreover, several other quinolone antibacterial agents appear to be taken up by the same transporter in lung cells, and the lipophilicity of the quinolones may contribute to the affinity for the transporter. At therapeutic concentrations, the lung uptake of HSR-903 can be at least partially accounted for by this carrier-mediated active transport mechanism.

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References


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