Carrier-Mediated Absorption of Salicylic Acid from Hamster Cheek Pouch Mucosa

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Abstract □ Previously, we found that monocarboxylic acids undergo carrier-mediated transport in primary cultures of oral mucosal epithelial cells.[1] In this study, we investigated whether carrier-mediated absorption of a monocarboxylic acid from the oral mucosa occurs in vivo. Salicylic acid was administered to hamster cheek pouch. At predetermined intervals, the concentration of salicylic acid in the fluid remaining in the cheek pouch lumen and the blood salicylic acid concentration were determined. The absorption of salicylic acid was saturable at high salicylic acid concentrations. Sodium azide, a metabolic inhibitor, and carbonylcyanide *p*-trifluoromethoxyphenylhydrazone (FCCP), a protonophore, significantly inhibited the absorption of salicylic acid but not the absorption of salicylamide from the oral mucosa. Various monocarboxylic acids inhibited the absorption of salicylic acid, whereas dicarboxylic acids had no such effect. Transfer of [^{14}C]salicylic acid from the cheek pouch mucosa to the systemic circulation was observed, and the blood [^{14}C]salicylic acid concentration in the case of coadministration with propionic acid was significantly lower than that in the case of no propionic acid coadministration. These results show that monocarboxylic acids undergo carrier-mediated absorption from the hamster cheek pouch mucosa.

Introduction

The oral mucosal route is advantageous for drug delivery into the systemic circulation because exposure of the administered drug to gastrointestinal juices and its hepatic first-pass elimination are prevented.[2] In general, the absorption of drugs from the oral mucosa can be explained in terms of the pH−partition hypothesis, which is well illustrated by passive diffusion mechanisms.[3] The hypothesis proposes that the rate of drug absorption depends on the percentage of drug molecules ionized and the lipid solubility of nonionized drug molecules. However, in vivo studies have revealed that some drugs undergo carrier-mediated absorption from the oral mucosa.[4,5] In previous studies, we demonstrated that a carrier-mediated transport system for monocarboxylic acids exists in rabbit oral mucosal epithelial cells in primary culture.[1] However, no data are currently available indicating that carrier-mediated monocarboxylic acid absorption occurs in vivo. In the present study, we investigated whether carrier-mediated drug absorption from hamster cheek pouch mucosa occurs in vivo.

Experimental Section

Materials—[^{14}C]Salicylic acid (55 Ci/mol) was obtained from American Radiolabeled Chemicals (St. Louis, MO). MCDB 153, an epidermal growth factor, and trypsin type III were obtained from Sigma Chemicals (St. Louis, MO). Fetal calf serum (FCS) was purchased from Biotech International Ltd. (Australia). Dispase II was obtained from Boehringer Mannheim (Germany). Tissue culture plates were purchased from Costar (Cambridge, MA). 2-Morpholinoethanesulfonic acid, monohydrate (MES) and *N*-[2-hydroxyethyl]piperazine-*N*′-[2-ethanesulfonic acid] (HEPES) were purchased from Dojin (Kumamoto, Japan). All other chemicals were of the highest available purity and analytical grade, and were purchased from Wako Pure Chemical Industries (Osaka, Japan)

Cell Culture—Oral mucosal epithelial cells were isolated from hamster cheek pouch mucosa and cultured by a previously described method[1] with slight modifications. Briefly, golden hamsters (body weight range, 180−220 g) were sacrificed by the administration of sodium pentobarbital, and their buccae were excised, washed with phosphate-buffered saline (PBS) containing antibiotics (penicillin G, 200 U/mL; streptomycin, 200 μg/mL; and gentamicin, 40 μg/mL), and then cut with a razor into small pieces (each about 3 × 6 mm in size). The tissue pieces were then incubated at 4 °C in Dispase II solution (2.4 U/mL) containing the antibiotics. After a 36-h incubation, the epithelial cell sheets were separated using forceps and centrifuged for 5 min at 200 x *g*. The cell pellets were suspended in a low Ca^{2+} medium, MCDB 153, supplemented with FCS (10%), insulin (5 μg/mL), transferrin (10 μg/mL), phosphorylethanolamine (14.1 μg/mL), penicillin G (100 U/mL), streptomycin (100 μg/mL), gentamicin (20 μg/mL), and epidermal growth factor (10 ng/mL). The resultant suspension was plated onto the wells in a collagen-coated 12-well tissue culture plates. After 24 h of cultivation at 37 °C in a 95% air:5% CO_2 humidified atmosphere, the cells were washed twice with PBS and fresh culture medium was added to each well. After 4 or 5 days of cultivation, drug uptake experiments were performed. The cell type was identified and the purity of the cell preparation was determined by indirect immunofluorescence staining of keratin.[6] More than 95% of the cells were positively stained for keratin (data not shown).

Uptake Experiments—The hamster oral mucosal epithelial cells (HOEpi) were washed twice with Hanks' balanced salt solution (HBSS; 136.7 mM NaCl, 0.385 mM Na_2HPO_4, 0.441 mM KH_2PO_4, 0.952 mM $CaCl_2$, 5.36 mM KCl, 0.812 mM $MgSO_4$, 25 mM D-glucose, and 10 mM MES for adjustment of pH to 5.0) before a test solution containing [^{14}C]salicylic acid was added. [^{14}C]-Salicylic acid (0.25 μCi/mL; 4.5 μM) was used as a marker for monocarboxylic acid carrier-mediated transport. The pH of the test solution was 5.0 except in pH-dependent uptake experiments. In pH-dependent experiments, the pH range of the incubation buffer was 5.0−7.5. The buffer solutions were prepared by adding MES (pH 5.0−6.5) or HEPES (pH 7.0−7.5) to HBSS. After 30 s, the test solution was aspirated and the cells were washed four times with ice-cold HBSS. For quantitation of [^{14}C]salicylic acid uptake, the cells were suspended in 0.5 N NaOH (300 μL) and the suspension was incubated at 37 °C for 12 h at which point 1.0 N HCl (150 μL) was added. The remaining radioactivity was quantified using a liquid scintillation counter (Aloka, LSC-5100). Cellular protein was quantified using a protein assay kit (Bio-Rad, CA), with bovine serum albumin as the standard. Details of the conditions for each experiment are given in the figure legends or table footnotes.

Data Analysis—The kinetic parameters of saturable uptake by HOEpi were determined using a nonlinear least squares

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regression analysis program, MULTI.[7] The uptake rate (J) was fitted to the following equation, which consists of both saturable and nonsaturable linear terms:

$$J = J_{max} \times C/(Kt + C) + k \times C \quad (1)$$

where J_{max} is the maximum uptake rate for a carrier-mediated process, C is the salicylic acid concentration, K_t is the half-saturation concentration (Michaelis constant), and k is a first-order rate constant.

In Vivo Absorption Experiments—The in vivo absorption experiments were performed using a slightly modified version of a method described previously.[3] Briefly, male golden hamsters (body weight range, 120−150 g) were anesthetized with urethane (1.5 g/kg, ip) and fastened onto a platform tilted at an angle of 55°. The cheek pouch was cleaned by multiple saline rinses. A vinyl tube (o.d., 1.2 mm; i.d., 0.8 mm; Natsume, Japan) was inserted into the cheek pouch to a depth of 50 mm. One milliliter of the drug solution (20 μM) dissolved in buffer was administered into the cheek pouch. In pH-dependent absorption experiments, the buffer pH ranged from 3.0 to 7.0. Buffer solutions of pH 6.0 were prepared by adding MES to HBSS, whereas for the pH 7.0 buffer solution, HEPES was added to HBSS. Citric acid−Na_2HPO_4 buffer was used for the pH 3.0−5.0 experiments. For other experiments also, citric acid−Na_2HPO_4 buffer (pH 5.0) was used. At predetermined time points after the drug administration, the fluid in the cheek pouch lumen was collected. The amount of the drug present in the fluid was determined by fluorescence (salicylic acid: Ex. 300 nm, Em. 430 nm) or UV (salicylamide: 235 nm) detectors. The reduction in concentration of the drug in the cheek pouch was used as a measure of the apparent absorption.

Plasma Concentration of Salicylic Acid—Under anesthesia, [^{14}C]salicylic acid solution (2.0 μCi/mL; 36 μM) was administered into the cheek pouch lumen. At predetermined time points after the administration, blood samples were collected from the ophthalmic vessels using a glass capillary coated with heparin (DURAN ringcaps, Germany). Each blood sample was placed in a scintillation vial to which 0.2 mL of perchloric acid solution was added. After vigorous shaking, 0.3 mL of hydrogen peroxide solution was added. After 30 min of incubation at 70 °C, scintillation cocktail (Clear-sol II, Nacalai Tesque, Japan) was added. Radioactivity was quantified using a liquid scintillation counter.

Statistical Analysis—All results were expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was used for single and multiple comparisons. Values of p of 0.05 or less were considered to indicate statistical significance.

Results

Salicylic Acid Uptake by HOEpi—We reported previously on monocarboxylic acid transport across oral mucosal epithelial cells using cultured epithelial cells from rabbit oral mucosa.[1] The hamster is most widely used for studies of drug absorption from the oral mucosa. In the present study, we first determined whether a carrier-mediated monocarboxylic acid transport system exists in cultured hamster oral epithelial cells.

Concentration and Temperature Dependence of Salicylic Acid Uptake—The effect of incubation temperature on the rate of uptake of [^{14}C]salicylic acid by HOEpi was studied. The rate of uptake was much lower at 4 °C than at 37 °C, as shown in Figure 1. Figure 1 also shows the relationship between the initial rate of uptake of [^{14}C]-salicylic acid and its concentration in the incubation medium. The results indicate that the uptake of salicylic acid consists of two processes, a saturable process evident at low concentrations and an apparently nonsaturable process evident at high concentrations. The uptake processes were analyzed using eq 1. The kinetic parameters calculated for salicylic acid uptake were a J_{max} of 140 ± 16 nmol/30 s/mg protein, a K_t of 0.14 ± 0.03 mM, and a k of 33 ± 3 μL/30 s/mg protein.

Energy and Proton-Gradient Dependence of Salicylic Acid Uptake—The effect of a metabolic inhibitor on the uptake of [^{14}C]salicylic acid was studied to determine whether this uptake requires metabolic energy (Table 1). Sodium azide (10 mM), a metabolic inhibitor, inhibited the uptake of [^{14}C]salicylic acid by HOEpi. Carbonylcyanide *p*-trifluoromethoxyphenylhydrazone (FCCP; 50 μM), a protonophore, also significantly inhibited the uptake. These findings suggest that [^{14}C]salicylic acid uptake by HOEpi is energy- and proton-gradient-dependent.

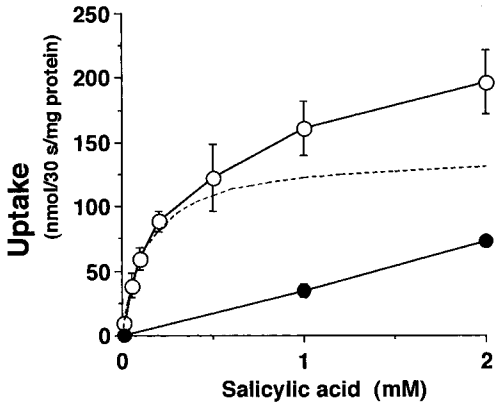

Figure 1—Concentration and temperature dependence of [^{14}C]salicylic acid uptake by HOEpi. The rate of uptake of [^{14}C]salicylic acid by HOEpi was measured at (○) 37 °C and (●) 4 °C. The dotted line represents the saturable component of the uptake of salicylic acid calculated from the kinetic parameters determined as described in the text. The vertical bar through each point represents the SD for four experiments.

Table 1—Effects of a Metabolic Inhibitor, a Protonophore, and Various Carboxylic Acids on [^{14}C]Salicylic Acid Uptake by HOEpi

variable type	compound	relative uptake (% of control)
metabolic inhibitor	sodium azide[a]	33.3 ± 8.7[b]
protonophore	FCCP[a]	15.9 ± 10.1[b]
monocarboxylic acid	*n*-butyric acid	8.0 ± 1.4[b]
	propionic acid	9.9 ± 3.0[b]
	valproic acid	12.2 ± 6.9[b]
	acetic acid	17.0 ± 8.2[b]
	lactic acid	46.6 ± 17.6[b]
	pyruvic acid	50.6 ± 4.6[b]
dicarboxylic acid	glutaric acid	95.4 ± 17.9
	fumaric acid	107.6 ± 37.5
	maleic acid	99.4 ± 24.0

[a] HOEpi were pretreated with sodium azide (10 mM) or FCCP (50 μM) for 15 min; all carboxylic acids were tested at 10 mM. [b] Significantly different from the control value ($p < 0.05$).

pH-Dependent Uptake—Figure 2 illustrates the effect of incubation buffer pH in the range of 5.0 to 7.5 on [^{14}C]-salicylic acid uptake by HOEpi. The rate of [^{14}C]salicylic acid uptake increased with decreasing pH from neutral to acidic. At pH 7.5, little salicylic acid uptake was observed. In the presence of 10 mM unlabeled salicylic acid, the uptake of [^{14}C]salicylic acid was significantly reduced and almost completely suppressed. The inhibitory effect of unlabeled salicylic acid increased with decreasing pH from neutral to acidic, suggesting that the passive diffusion route is a minor route and carrier-mediated transport is the major mechanism involved in the uptake of salicylic acid. Previous studies in our laboratory have shown the existence of pH-dependent, monocarboxylic acid transport in the rabbit oral mucosal epithelial cells.[1] In the present study, we also showed that FCCP inhibited the uptake of salicylic acid by HOEpi (Table 1). Our data suggest that carrier-mediated salicylic acid uptake by HOEpi is proton-gradient-dependent, implying that an acidic pH is suitable for the evaluation of monocarboxylic acid transport in HOEpi.

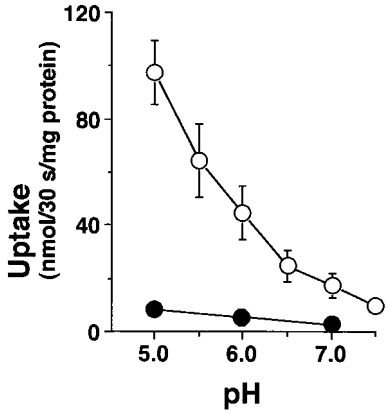

Figure 2—pH Dependence of [^{14}C]salicylic acid uptake by HOEpi. Uptake of [^{14}C]salicylic acid by HOEpi was measured at 37 °C in the (○) absence and (●) presence of 10 mM unlabeled salicylic acid. The vertical bar through each point represents the SD for four experiments.

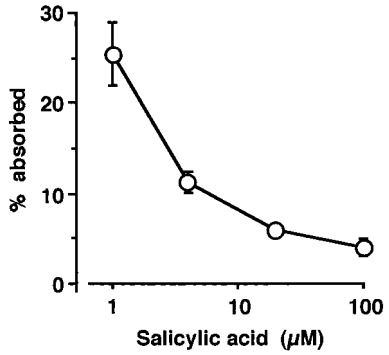

Figure 3—Concentration dependence of salicylic acid absorption. Salicylic acid (1–100 μM) was administered into a hamster cheek pouch. After 15 min, the fluid in the cheek pouch was collected and the amount of salicylic acid present in the fluid was measured. The reduction in concentration of the salicylic acid in the lumen of the cheek pouch was used as a measure of the apparent absorption. The vertical bar through each point represents the SD for four experiments.

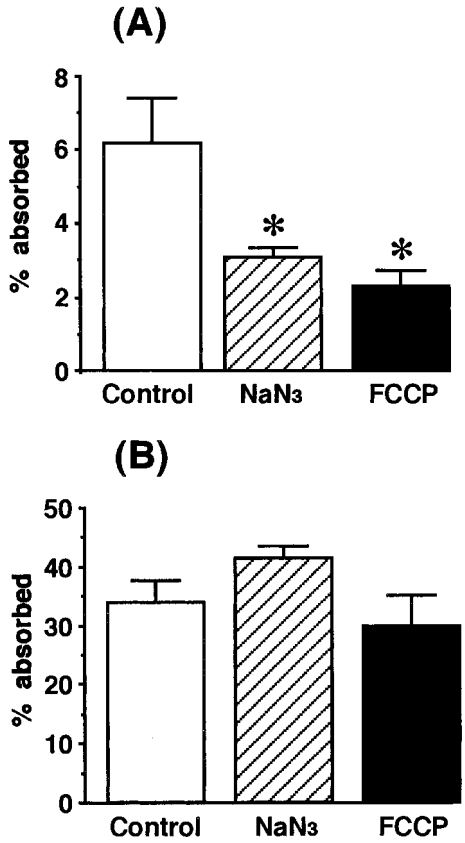

Figure 4—Effects of metabolic inhibitor and protonophore on (A) salicylic acid and (B) salicylamide absorption. A metabolic inhibitor (sodium azide, NaN_3, 10 mM) or a protonophore (FCCP, 50 μM) was administered into the hamster cheek pouch. After 15 min, salicylic acid (20 μM) or salicylamide (20 μM) was added. Then, 15 min later, the fluid in the cheek pouch was collected and the amount of salicylic acid or salicylamide present in the fluid was measured. The disappearance of salicylic acid and salicylamide from the lumen of the oral cavity was defined as the apparent absorption. The vertical bar through each point represents the SD for 3–5 experiments. The asterisk (*) indicates significantly different from the control ($p < 0.05$).

Therefore, a pH 5.0 buffer was used for subsequent experiments.

Specificity of the Carrier—To investigate the properties of the carrier involved in [^{14}C]salicylic acid uptake by HOEpi, we studied the effects of various mono- and dicarboxylic acids on this uptake (Table 1). Each monocarboxylic acid significantly inhibited the uptake of [^{14}C]-salicylic acid, whereas none of the dicarboxylic acids had any significant effect. These results imply that the carrier that mediates monocarboxylic acid uptake by HOEpi is a nonspecific monocarboxylic acid carrier.

Salicylic Acid Absorption from the Oral Mucosa In Vivo—We determined whether a monocarboxylic acid transport system exists in hamster cheek pouch mucosa in vivo.

Concentration Dependence of Salicylic Acid Absorption—The effect of luminal concentration of salicylic acid in the hamster cheek pouch on its absorption from the cheek pouch was examined in the concentration range of 1.0 to 100 μM. The percentages of the apparent absorption at 15 min and pH 5.0 are shown in Figure 3. At high concentrations of salicylic acid, the apparent absorption was saturated.

Energy and Proton-Gradient Dependence of Salicylic Acid Absorption—The effects of a metabolic inhibitor and a protonophore on the absorption of salicylic acid were studied (Figure 4). Both sodium azide (10 mM) and FCCP (50 μM) significantly inhibited the apparent absorption of salicylic acid from the oral mucosa. However, neither sodium azide nor FCCP affected the apparent absorption of salicylamide. These findings suggest that salicylic acid absorption from hamster oral mucosa is carrier-mediated and depends on the proton gradient and energy.

pH-Dependent Uptake—Figure 5 illustrates the effect of buffer pH in the range of 3.0 to 7.0 on salicylic acid absorption from hamster oral mucosa. The apparent absorption of salicylic acid increased with decreasing pH from neutral to acidic. In the present study, we also showed that FCCP inhibited the absorption of salicylic acid from hamster oral mucosa (Figure 4). These data suggest that salicylic acid absorption is proton-gradient-dependent, implying that an acidic pH is suitable for the evaluation of a monocarboxylic acid transport system in hamster oral mucosa. However, at very low values of pH (e.g., 3.0 or 4.0), most of the salicylic acid in solution exists in the nonionized form. An increase in the fraction of nonionized salicylic acid resulted in an increase in the passive diffusion of salicylic acid across the oral mucosa. Therefore, pH 5.0 buffer was used for subsequent absorption experiments.

Specificity of the Carrier—To investigate the properties of the carrier involved in salicylic acid absorption from hamster oral mucosa, we studied the effects of various mono- and dicarboxylic acids on this absorption (Table 2). Each monocarboxylic acid tested significantly inhibited the apparent absorption of salicylic acid, whereas none of the dicarboxylic acids had any significant effect. These results

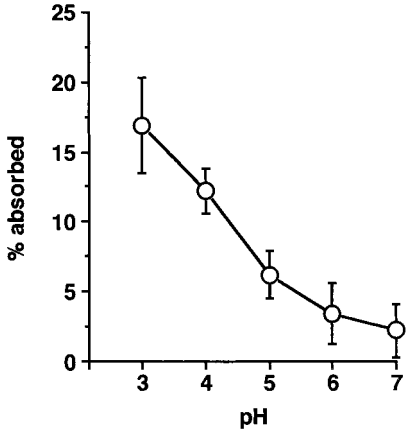

Figure 5—The pH dependence of salicylic acid absorption. Salicylic acid dissolved in various pH buffers (pH 3.0–7.0) was administered into the hamster cheek pouch. After 15 min, the fluid in the cheek pouch was collected and the amount of salicylic acid present in the fluid was measured. The disappearance of salicylic acid from the lumen of the oral cavity was defined as the apparent absorption. The vertical bar through each point represents the SD for four experiments.

Table 2—Effects of Various Carboxylic Acids on Salicylic Acid Absorption from Hamster Cheek Pouch Mucosa[a]

variable type	compound	relative absorption (% of control)
monocarboxylic acid	*n*-butyric acid	22.0 ± 15.3[b]
	propionic acid	7.3 ± 2.6[b]
	valproic acid	45.6 ± 1.5[b]
	acetic acid	14.4 ± 7.6[b]
dicarboxylic acid	glutaric acid	102.5 ± 17.8
	fumaric acid	78.0 ± 27.1
	maleic acid	93.2 ± 8.5

[a] All carboxylic acids were tested at 10 mM. [b] Significantly different from the control value ($p < 0.05$).

suggest that the carrier that mediates monocarboxylic acid absorption is a nonspecific monocarboxylic acid carrier.

Blood Concentration—We further examined whether the [^{14}C]salicylic acid that disappeared from the oral mucosal lumen was transferred to the systemic circulation. The blood concentration−time profiles of [^{14}C]salicylic acid following intracheek pouch administration in the presence and absence of propionic acid (10 mM) are shown in Figure 6. Transfer of [^{14}C]salicylic acid to the systemic circulation was detected. The blood concentration versus time curves demonstrate that propionic acid significantly inhibited the absorption of salicylic acid from the oral mucosa.

Discussion

In previous studies, we demonstrated that carrier-mediated monocarboxylic acid transport systems exist in rabbit oral mucosal epithelial cells in primary culture.[1] However, carrier-mediated absorption of monocarboxylic acids from the oral mucosa in vivo had not been previously described. In the present study, we demonstrated the existence of a carrier-mediated transport system for monocarboxylic acids in the oral mucosa in vivo.

Salicylic acid uptake by HOEpi is characterized as follows: (a) reduction of the incubation temperature from 37 to 4 °C markedly inhibited the uptake; (b) salicylic acid uptake was saturable at high concentrations; (c) a metabolic inhibitor and a protonophore significantly inhibited the uptake, indicating that this uptake process is energy- and proton-gradient-dependent; and (d) monocarboxylic acids significantly inhibited the uptake of salicylic acid.

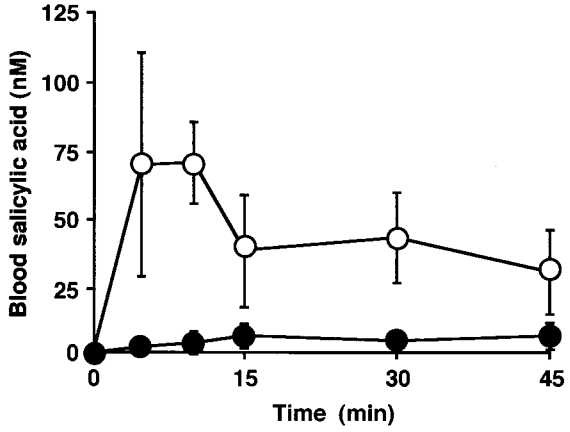

Figure 6—Blood concentration of [^{14}C]salicylic acid after intracheek pouch administration of [^{14}C]salicylic acid (●) with or (○) without 10 mM propionic acid. [^{14}C]Salicylic acid (2.0 μCi/mL; 36 μM) was administered into the hamster cheek pouch. Blood was collected from the ophthalmic vessels. The vertical bar through each point represents the SD for four experiments.

These characteristics of monocarboxylic acid uptake by HOEpi are similar to those observed in rabbit oral mucosal epithelial cells. These data demonstrate the existence of a carrier-mediated monocarboxylic acid transport system in HOEpi.

We also demonstrated carrier-mediated salicylic acid absorption from hamster cheek pouch mucosa. The apparent absorption of salicylic acid from the hamster cheek pouch mucosa in vivo is characterized as follows: (a) the apparent absorption of salicylic acid was saturable at a high initial concentration; (b) a metabolic inhibitor and a protonophore significantly inhibited salicylic acid apparent absorption, indicating that this apparent absorption is energy- and proton-gradient-dependent; and (c) monocarboxylic acids significantly inhibited the salicylic acid apparent absorption. These observations of monocarboxylic acid absorption in vivo are similar to those in vitro and strongly suggest the occurrence of carrier-mediated monocarboxylic acid transport in hamsters in vivo.

Moreover, the present study confirms the transfer of [^{14}C]-salicylic acid from the oral mucosa to the systemic circulation (Figure 6). These data demonstrate that salicylic acid that disappeared from the oral luminal cavity did not remain in the mucosal tissue but was transferred to the blood. Coadministration of propionic acid significantly reduced the blood concentration of [^{14}C]salicylic acid. Passive absorption of salicylic acid was not inhibited by coadministered propionic acid. Therefore, the coexistence of propionic acid with the absorbed salicylic acid indicates passive absorption. Figure 6 also shows that the rate of passive absorption of [^{14}C]salicylic acid from the oral luminal cavity is much lower than that of carrier-mediated absorption of [^{14}C]salicylic acid.

The surface of hamster cheek pouch mucosa is keratinized.[8] Therefore, no carrier-mediated transport occurs across this keratinized part because keratinized cell layers consist of differentiated dead cells. However, our data indicate that carrier-mediated absorption occurs in the hamster cheek pouch mucosa. This result may explain why the keratinized layer is not the main barrier to salicylic acid transport. Salicylic acid may be transported via a carrier-mediated system in the living epithelial cell layers that are located under the keratinized cell layers.

Figures 2 and 5 show pH-dependent uptake or absorption of salicylic acid. At neutral pH, little uptake was observed. However, the uptake of salicylic acid increases with a decrease of pH. Salicylic acid is an acidic compound; therefore, a decrease in pH increases the fraction of

nonionized salicylic acid. According to the pH−partition hypothesis, this increase in the fraction of nonionized form increases the passive absorption of salicylic acid across the oral mucosa. These data (Figures 2 and 5) alone are insufficient to conclude that the uptake of salicylic acid is proton-gradient-dependent. However, it is evident from Table 1 and Figure 4 that FCCP, a protonophore, inhibited the uptake of salicylic acid. These results strongly suggest that salicylic acid uptake is proton-gradient-dependent.

In in vitro experiments (Figure 1), the K_t of salicylic acid was 0.14 ± 0.03 mM. However, in in vivo experiments (Figure 3), the absorption of salicylic acid was saturated at 0.1 mM or less. We have no clear explanation as to why the saturation behavior is different between in vitro and in vivo conditions. There are some differences between in vivo and in vitro states. In vitro, salicylic acid transport was studied in terms of its uptake by cultured epithelial cell monolayers. This means that only the transport of salicylic acid from the apical side to intercellular spaces was evaluated. On the other hand, in vivo, the apparent absorption as determined by its disappearance from the hamster cheek pouch, by the oral mucosa which consists of multilayer epithelial cells was evaluated. The difference in results may be due to differences between cultured cells and cells in vivo, uptake and transport, and monolayer and multilayer.

Figure 4 shows that both sodium azide (10 mM) and FCCP (50 μM) significantly inhibit the apparent absorption of salicylic acid from the oral mucosa. However, neither sodium azide nor FCCP affected the apparent absorption of salicylamide. These findings suggest that salicylic acid absorption from hamster oral mucosa is carrier-mediated and depends on the proton gradient and energy. However, the absorption of salicylamide (the control) is six times higher than that of salicylic acid. The difference in the apparent absorption values between salicylamide and salicylic acid could be due to the differences in their lipophilicities. The apparent octanol−buffer (pH 5.0) distribution coefficient of salicylic acid at 37 °C is 0.45 ± 0.02, and that of salicylamide is 14.56 ± 0.09 (these results were obtained in our laboratory, although details of the experimental conditions are not shown). Salicylamide is 32 times more lipophilic than salicylic acid at pH 5.0, which may account for its higher apparent absorption.

The rate of absorption of a drug from the hamster cheek pouch mucosa is related to the lipophilicity of the drug.[3] A lipophilic index based on the results of reversed-phase HPLC has been used extensively as a measure of the lipophilicity of drugs.[9] Kurosaki et al. reported[3] that the lipophilic index of salicylic acid is the same as that of phenacetin. However, the absorption rate of salicylic acid from the hamster cheek pouch mucosa is about three times higher than that of phenacetin (48.6 ± 4.1 and 16.0 ± 0.6%, respectively, after 1 h). Kurosaki et al. did not discuss this finding in their report.[3] This higher percentage absorption of salicylic acid than that of phenacetin may be accounted for by carrier-mediated absorption of salicylic acid from the hamster cheek pouch mucosa.

Our present results suggest that drugs that have a monocarboxylic acid residue could potentially be delivered into the systemic circulation from the oral mucosa via carriers. This carrier-mediated oral mucosal absorption route may serve as a new approach for drug absorption from the oral mucosa.

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