Differences in the Enhancing Effects of Sodium Caprate on Colonic and Jejunal Drug Absorption

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We examined the enhancing effect of sodium caprate (C10) on the jejunal absorption of a poorly absorbed drug, cefmetazole, in rats, in comparison with its colonic absorption (*Pharm. Res.* 5, 341–346, 1988). Jejunal absorption was significantly enhanced by C10, but to a smaller extent than colonic absorption. Membrane perturbation, caused by the interaction between C10 and membrane proteins or lipids, was shown to increase transcellular drug permeability, as reported in the colon. Paracellular permeabilities, obtained from the permeabilities of water-soluble nonelectrolytes of various molecular weights, showed a two-phase pattern against their free diffusion coefficients, suggesting the existence of at least two pore routes similar to those in the colon. C10 increased paracellular permeability in the colon but not in the jejunum. Impedance analysis and voltage clamp technique in the jejunum showed no significant effect of C10 on paracellular permeability, such as found in the colon. Accordingly, the difference in the effects of C10 on the jejunal and colonic absorption of cefmetazole was due mainly to the difference in its effects on the paracellular pathway.

KEY WORDS: jejunal absorption; colonic absorption; absorption enhancer; transcellular pathway; paracellular pathway; sodium caprate.

INTRODUCTION

Transepithelial drug transport occurs through the transcellular pathway of the lipoidal cell membrane and the paracellular pathway from the tight junction to the lateral intercellular space (1). We have shown that colonic absorption of the poorly absorbed drug, cefmetazole, was enhanced by sodium caprate (C10)[4] through both the transcellular pathway (2) and the paracellular pathway in the rat (3). As evidence of the increase in colonic transcellular permeability, using the brush border membrane (BBM) vesicles of the rat colon (2), we found (i) membrane perturbation caused by the interaction between C10 and membrane proteins or lipids and (ii) an increase in the release of poorly absorbed 5(6)-carboxyfluorescein (CF) (previously entrapped in the BBM vesicles) in the presence of C10. For the paracellular pathway, the increase in the equivalent pore radius was obtained from the ratio of osmotic permeability to diffusive permeability of water in the everted sac of the rat colon (3).

In this study, the enhancing effect of C10 on the jejunal absorption of cefmetazole in rats was examined and compared with the above results in the colon. For studying the transcellular pathway, the perturbation of membrane proteins and lipids by C10 and the increase in CF permeability induced by C10 were examined in the jejunal BBM vesicles of rats. Also for studying the paracellular pathway, the following three values were determined: (i) the permeability of water-soluble nonelectrolytes of various molecular weights through the jejunal membrane; (ii) cefmetazole permeability through the jejunal and colonic membranes by the voltage clamp technique; and (iii) impedance of the jejunal membrane.

MATERIALS AND METHODS

Chemicals

C10 and sodium caprylate (C8) were purchased from Tokyo Kasei Kogyo, Tokyo. The fluorescent probes used and their sources were: 2-(9-anthroyloxyl)-stearic acid (2-AS) from Molecular Probes Inc., Junction City, Ore.; 1,6-diphenyl-1,3,5-hexatriene (DPH) from Tokyo Kasei Kogyo, Tokyo; and fluorescein isothiocyanate (FITC) and dansyl chloride (DNS-Cl) from Sigma Chemical Co., St Louis, Mo. CF was obtained from Eastman Kodak Co., Rochester, N.Y. Hyaluronidase (Type 1-S) for preparation of jejunal BBM vesicles and bovine serum albumin (fraction V) for protein determination were obtained from Sigma Chemical Co., St. Louis, Mo. [^{14}C]Urea, [^{14}C]thiourea, [^{14}C]glycerol, [^{14}C]mannitol, [^{3}H]polyethylene glycol 900 (PEG 900), [^{3}H]inulin, and *n*-[^{14}C]butanol were purchased from New England Nuclear, Boston, Mass. Cefmetazole and [^{14}C]cefmetazole were kindly supplied by Sankyo Co., Tokyo. All other reagents were of analytical grade or better.

In Situ Absorption Experiment

Male Wistar rats (200 ± 20 g), fasted overnight, were anesthetized by administering ethyl carbamate (1.1 mg/kg) intraperitoneally. The absorption of cefmetazole was examined in the rat by the *in situ* jejunal loop technique in the same manner as absorption had been examined in the colon (2,3). At the end of the duodenum and 8 cm distal from that, proximal and distal cannulas, respectively, were inserted according to the method of Doluisio *et al.* (4). The jugular vein was also cannulated to obtain blood samples. The luminal solution consisted of a 50 m*M* isotonic phosphate buffer solution (Na_2HPO_4 + KH_2PO_4, pH 6.5) with 0.25% enhancer

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[4] Abbreviations used: BBM, brush border membrane; C10, sodium caprate; C8, sodium caprylate; CF, 5(6)-carboxyfluorescein; DPH, 1,6-diphenyl-1,3,5-hexcatriene; 2-AS, 2-(9-anthroyloxy)-stearic acid; FITC, fluorescein isothiocyanate; DNS-Cl, 1-dimethylaminonaphthalene-5-sulfonyl chloride; PEG 900, polyethylene glycol 900; AUC, area under the plasma concentration–time curve; *P*, fluorescence polarization; P_m, membrane permeation clearance corrected for the unstirred water layer; D_{fr}, free diffusion coefficient; R_j, resistance of the intercellular junctions; R_L, resistance of lateral intercellular spaces; C_M, membrane capacitance; ΔPD, potential difference

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(C10 or C8) and 1% cefmetazole. Only plasma cefmetazole concentration was assayed. Blood sampling and pretreatment of the samples prior to HPLC cefmetazole analysis were carried out as in our previous report (3).

Preparation of BBM Vesicles from Rat Jejunum

BBM vesicles were prepared by the method of Kessler *et al.* (5) from the jejunum (about 30 cm from the end of the duodenum) of a male Wistar rat (200 ± 20 g) fasted overnight. The activities of marker enzymes and the protein concentration in the vesicles were determined in the manner reported by Kajii *et al.* (2,6).

Fluorescent Probe Labeling of BBM Vesicles and Measurement of Fluorescence Polarization

Labeling of BBM vesicles by fluorescent probes and measurements of their fluorescence polarization (P) values were conducted according to the method of Kajii *et al.* (2,6). Vesicles containing 4–6 mg of protein, prepared from two rats, were used for each experiment, which was conducted with one promoter and one fluorescent probe. The excitation and emission wavelengths were 380 and 455 nm for DPH, 390 and 445 nm for 2-AS, and 497 and 528 nm for FITC, respectively.

Release of CF from the BBM Vesicles

Preparation of BBM vesicles containing CF and measurement of the release of CF from the vesicles were carried out according to the method of Kajii *et al.* (2,6). The release experiments were performed at 25°C to minimize spontaneous leakage of CF from the vesicles. The fluorescence intensity of CF released from the vesicles was measured directly without separation from the vesicles, since CF in the vesicles scarcely emits fluorescence by self-quenching. The excitation and emission wavelengths were 490 and 520 nm, respectively. The emitted light was passed through a 510-nm cutoff filter.

In Vitro Membrane Permeation Experiment

The detailed method followed that of Sawada *et al.* (7). Male Wistar rats (250 ± 20 g) and New Zealand white rabbits (2.5 ± 0.5 kg) were used after being fasted overnight. Rat and rabbit jejunal mucosa, 10–15 cm distal from the end of the duodenum, was mounted in an Ussing-type chamber (0.75-cm^2 exposed surface, 11-ml inner volume) as a flat sheet. Since the underlying muscle of rat jejunum is too thin to be stripped, the rat jejunal sheet was mounted without stripping. One jejunal segment was prepared from one rat, and one or two jejunal segments were prepared from one rabbit. The permeation experiment was performed both in the presence of C10 and in its absence (control) at 37°C. Apparent permeation clearances were obtained from the permeation rates of ^{14}C- or ^{3}H-labeled nonelectrolytes from the mucosal to the serosal sides divided by their initial mucosal concentrations (7). The clearances were corrected for the unstirred water layer, using *n*-butanol to calculate the permeation clearance (P_m), as reported previously (3,7). Unstirred water layer-limited diffusion of butanol is supported by Smulders and Wright (8) and Os and Slegers (9). The thickness of the unstirred water layer was about 1 mm irrespective of the presence of the promoters.

Impedance Analysis

Impedances of the rabbit jejunum were measured by a phase-sensitive detection method using a circuit connected with the Ussing-type chamber, as described previously (10). Preparation of the rabbit jejunum segment was the same as for the permeation experiment. Steady-state impedances at frequencies of 0.015–30 kHz were measured both in the presence of C10 and in its absence (control) on the mucosal side. The model for impedance analysis (shown in Fig. 1), as applied to the small intestine by Pappenheimer (11), consisted of the resistance of the intercellular junctions (R_j) connected with the resistance of the lateral intercellular spaces (R_L) in a series, with the membrane capacitance in parallel (C_M). The impedance at low frequencies was equivalent to $R_j + R_L$; that at high frequencies was equivalent to R_L. Thus, from the relation between the impedance and the frequencies, we obtained the changes induced by C10 in the above electrical parameters.

Voltage Clamp Technique

Using the technique of Yamashita *et al.* (12), we mounted a sheet of rat colon, rat jejunum, or rabbit jejunum in the Ussing-type chamber. These tissues were from the animals fasted overnight, as described for the membrane permeation experiment. The rat colon and rabbit jejunum were stripped of underlying muscle prior to mounting. Ringer solution containing 3.5 μCi [^{14}C]cefmetazole, with or without 0.25% C10, was added to the mucosal side, and then the mucosal-to-serosal permeation rate was measured following a 10-min time lag. A transmural potential difference (ΔPD) was clamped to the arbitrary values (−20 to +30 mV) by applying electric fields externally; this condition was kept unchanged throughout the experiment (for 60 min). To de-

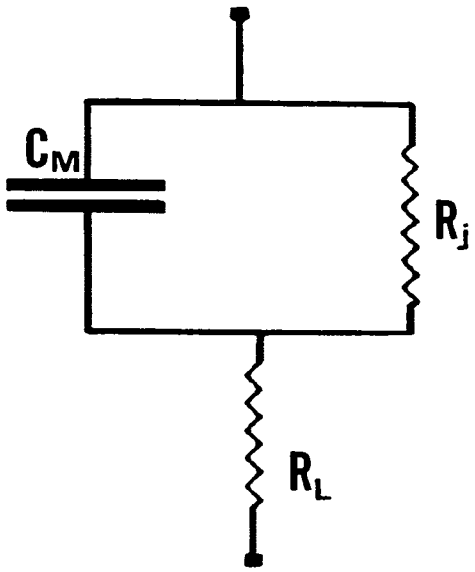

Fig. 1. Model for impedance analysis. R_j, intercellular junctional resistance; R_L, distributed resistance of the lateral intercellular spaces; C_M, lumped membrane capacitance.

termine the transcellular and paracellular permeabilities separately, the following relationship between P_m and ΔPD was used (13):

$$P_m = P_{m,trans} + (P_{m,para})_o \quad (1)$$

$$\xi = \exp(-z \cdot F \cdot \Delta PD/2 \cdot R \cdot T) \quad (2)$$

P_m values were obtained under this voltage clamp condition in the same manner as shown in the *in vitro* permeation experiment. $P_{m,trans}$ is the transcellular permeation clearance and $(P_{m,para})_o$ is the paracellular permeation clearance under the short-circuit condition ($\Delta PD = 0$). Definitions of z, F, R, and T have their conventional meanings. $P_{m,trans}$ and $(P_{m,para})_o$ are obtained as an intercept and a slope of linear relationship between P_m and ξ shown in Eq. (1), respectively, by linear regression analysis.

Assay

The plasma concentration of cefmetazole was measured by HPLC as reported by Sekine *et al.* (14). The ^3H and ^{14}C activities of cefmetazole and nonelectrolytes were counted by liquid scintillation counter (Aloka 903, Tokyo), as reported by Sawada *et al.* (7). The decrease in counting efficiency resulting from quenching was automatically corrected by the external standard source.

Statistical Analysis

Levels of statistical significance were asserted using Student's t test. Significant differences were judged as p values less than 0.05.

RESULTS

The plasma concentration of cefmetazole obtained by the *in situ* jejunal loop technique is shown in Fig. 2. The low cefmetazole absorption in the control was significantly enhanced by 0.25% C10 on the basis of AUC values ($p < 0.01$ versus the control). The effect of 0.25% C8 was so small that no significant difference from the control was detected. AUC from 0 to 60 min, calculated by the trapezoidal method using the plasma concentration data ($n = 6$) shown in Fig. 2, was 28.4 ± 2.7 μg min/ml in the control, 169 ± 18 μg min/ml in the presence of C10, and 34.0 ± 8.5 μg min/ml in the presence of C8. In contrast, AUC for colonic cefmetazole absorption corresponding to the cases above was reported as 26.2 ± 4.1 μg min/ml in the control, 263 ± 21 μg min/ml in the presence of C10, and 46.5 ± 0.3 μg min/ml in the presence of C8 (2). Thus, the enhancing effect of C10 or C8 on jejunal cefmetazole absorption was smaller than their effect on colonic absorption.

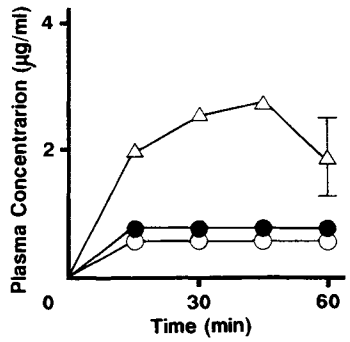

Fig. 2. Effects of 0.25% sodium caprate (△) and 0.25% sodium caprylate (●) on the jejunal absorption of cefmetazole. Open circles indicate data in the absence of enhancers (control). Each value represents the mean ± SE of six rats. For small SE, a bar is included in the symbol.

The decrease in P values, which is dependent on the enhancer concentration, was obtained and the decrease ratio at the enhancer concentration which is nearest to the *in situ* concentration (0.25%) is shown in Tables I and II. In Table I, P values of DPH and 2-AS-labeled jejunal BBM vesicles changed by 0.24% C10 or C8 are shown as decreased P value/control ratios. The data for colonic BBM vesicles reported previously (2) are also listed in Table I. DPH is considered to label the interior of the lipid layer and 2-AS, the exterior of the lipid bilayer situated closer to the aqueous interface. P values were significantly decreased by C10, but not by C8, with both DPH- and 2-AS-labeled vesicles in the jejunum. The results were quite similar to those in the colon. Table II shows the decreased ratios of P values induced by C10 or C8 in membrane protein in which the amino groups were labeled with FITC and DNS-Cl. The data for the colonic membrane in which amino groups were labeled with DNS-Cl (2) are also shown in Table II. Both C10 and C8 significantly decreased P values in the jejunum and the colon; the effect of C10 was greater than that of C8 in both jejunum and colon.

The enhancing effect at 20 min of C10 and C8 treatment on the cumulative release ratio of CF previously entrapped in BBM vesicles, which was obtained at the nearest enhancer concentration (0.21%) to the *in situ* concentration (0.25%), is shown in Table III together with the colonic data quoted from a previous paper (2). No CF release was detected in the control. The enhancing effect of C10 or C8 on CF release was greater in the jejunum than in the colon. Also, the enhancing effect of C10 was greater than that of C8.

In Fig. 3, the relationship between the P_m values of the

Table I. Effects of 0.24% Sodium Caprate (C10) and 0.24% Sodium Caprylate (C8) on the Fluorescence Polarization (P) of DPH-Labeled and 2-AS-Labeled BBM Vesicles from Rat Jejunum and Colon

	P value to the control (%)[a]	
	C10	C8
Jejunum		
DPH-labeled	67.1 ± 0.5*	96.4 ± 0.6
2-AS-labeled	95.7 ± 0.5*	100.5 ± 4.7
Colon[b]		
DPH-labeled	75.7 ± 0.4*	99.1 ± 3.1
2-AS-labeled	76.9 ± 0.5*	94.6 ± 4.4

[a] P value in the control labeled with DPH or 2-AS was 0.2–0.35. Each value represents the mean ± SE of at least three determinations.

[b] Data for the colon are quoted from Figs. 1 and 3 in a previous paper (2).

* Significantly lower than the control, at $p < 0.01$.

Table II. Effects of 0.24% Sodium Caprate (C10) and 0.24% Sodium Caprylate (C8) on the Fluorescence Polarization (*P*) of FITC-Labeled and DNS-Cl-Labeled BBM Vesicles from Rat Jejunum and Colon

	P value to the control (%)[a]	
	C10	C8
Jejunum		
FITC-labeled	49.1 ± 2.5*	74.4 ± 0.6*
DNS-Cl-labeled	71.8 ± 0.7*	80.9 ± 0.7*
Colon		
DNS-Cl-labeled	73.4 ± 0.2*	89.4 ± 1.0*

[a] *P* values in the controls labeled with FITC and DNS-Cl were 0.3–0.36 and 0.37–0.38, respectively. Each value represents the mean ± SE of at least three determinations.
[b] Data for the colon are quoted from Figs. 2 and 4 in a previous paper (2).
* Significantly lower than the control, at $p < 0.01$.

water-soluble nonelectrolytes across rat jejunal membrane and their free diffusion coefficient (D_{fr}) values is shown in the absence of enhancer (in the control). D_{fr} values were calculated by $D_{fr} \cdot (\text{molecular weight})^{0.5} = \text{constant}$ (15) and they have been listed previously (7). The linear relationship was obtained from inulin to mannitol and the P_m values of erythritol, glycerol, thiourea, and urea were greater than expected from the extrapolated linear values. These results suggest the existence of at least two pore routes in the paracellular pathway. Also, these data were very similar to the control data obtained in the colon, as reported previously (10), except that the cutoff position of the line was at mannitol in the jejunum and at erythritol in the colon. However, no enhancing effect of C10 or C8 on P_m was found in the jejunum, also shown in Fig. 3 ($p > 0.05$ versus the control). A similar two-phase pattern between the P_m and the D_{fr} of inulin, mannitol, and thiourea was found for the rabbit jejunal membrane (Fig. 4). These three compounds, inulin, mannitol, and thiourea, represented a high molecular weight compound, a compound at the cutoff position, and a compound with P_m greater than the expected linear value, respectively (Fig. 3). No enhancing effect of C10 on P_m was found in the rabbit jejunum ($p > 0.05$ versus the control).

The relationship between steady-state impedance and sine wave frequency of the rabbit jejunum is shown in Fig. 5. Rabbit jejunum was used since it was easily stripped of the underlying muscle; this removed muscle contribution to membrane impedance. Compared with data for the rat colon in a previous paper (8), changes in the impedance relating to low and high frequencies were found to be much smaller in the rabbit jejunum. The R_j value, which is the impedance difference between low and high frequencies, was about 10–20 $\Omega \cdot cm^2$ in the control. C10 had a tendency to decrease the impedance at high frequencies, but no significant effect of C10 on the relationship between impedance and frequency was found.

Table III. Release Ratio of 5(6)-Carboxyfluorescein (CF) from Jejunal and Colonic BBM Vesicles of Rats Increased by Treatment with 0.21% Sodium Caprate (C10) and 0.21% Sodium Caprylate (C8) for 20 min at 25°C

	Release ratio (%)[a]	
	C10	C8
Jejunum	51.9 ± 0.4	25.0 ± 2.0
Colon[b]	33.0 ± 0.6	6.1 ± 0.1

[a] Ratios to the total amount of CF entrapped in BBM vesicles. Values are means ± SE of three determinations.
[b] Data in the colon are quoted from Fig. 5 in a previous paper (2).

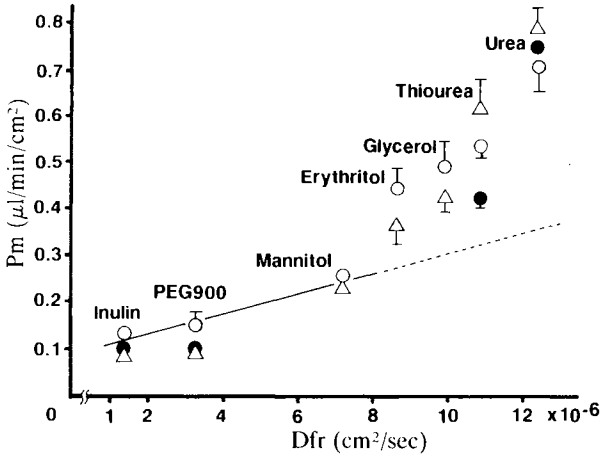

Fig. 3. Relationship between the permeation clearance (P_m) of nonelectrolytes through rat jejunal membrane and the free diffusion coefficients (D_{fr}). Each value represents the mean ± SE of five rats. For small SE, a bar is included in the symbol. No enhancing effect on P_m is found ($p > 0.05$ versus the control). (○) Control (in the absence of enhancer); (△) in the presence of 0.25% sodium caprate; (●) in the presence of 0.25% sodium caprylate.

The relationships between the P_m of cefmetazole and ξ values for the rat jejunal membrane, the rat colonic membrane, and the rabbit membrane are shown in Fig. 6. The P_m

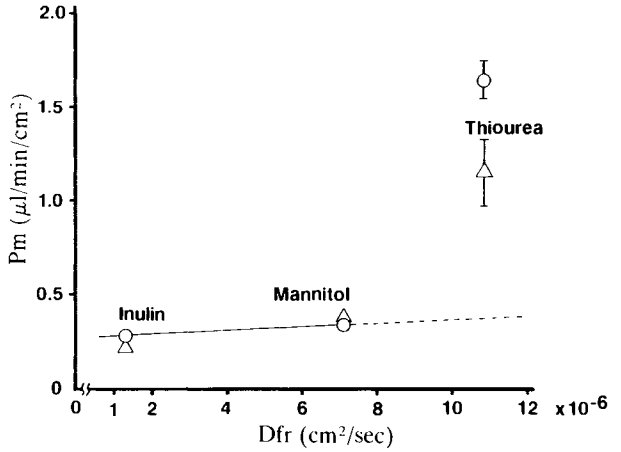

Fig. 4. Relationship between the permeation clearance (P_m) of nonelectrolytes through the rabbit jejunal membrane and the free diffusion coefficient (D_{fr}). Each value represents the mean ± SE of four to six determinations (more than three rabbits). For small SE, a bar is included in the symbol. No enhancing effect on P_m is found ($p > 0.05$ versus the control). (○) Control (in the absence of enhancer); (△) in the presence of 0.25% sodium caprate.

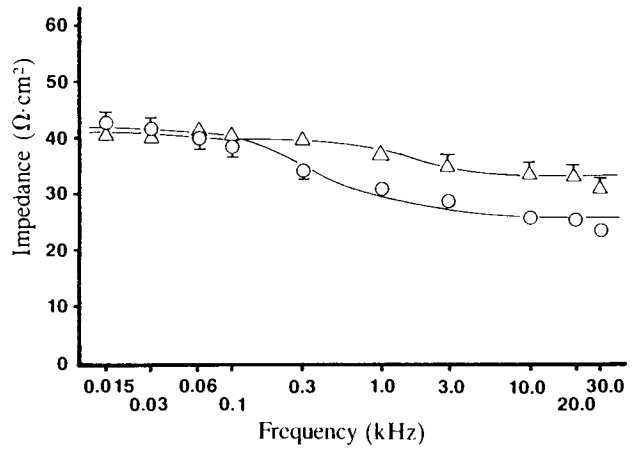

Fig. 5. Relationship between steady-state impedances and frequencies in the rabbit jejunum. Values represent the mean ± SE of five determinations (more than three rabbits). For small SE, a bar is included in the symbol. (○) Control (in the absence of enhancer); (△) in the presence of C10.

values in the control were smaller in the rat jejunum and colon than in the rabbit jejunum. In the rat colon, both $P_{m,trans}$ (0.0737 μl/min/cm^2) and $(P_{m,para})_o$ (0.0573 μl/min/cm^2) obtained by Eq. (1) were increased by C10 to 0.708 and 0.841 μl/min/cm^2, respectively. In contrast, no C10 effect was found in either the rat or the rabbit jejunum.

DISCUSSION

In our previous papers (2,3), we reported that colonic cefmetazole absorption was enhanced by C10. Comparing the results for the jejunum and colon, jejunal cefmetazole absorption was enhanced to a smaller extent by C10 than colonic absorption by C10 (Fig. 2). Perturbation of the BBM through interaction between C10 and membrane proteins or lipids was indicated by the decrease in the P values of the fluorescent probes labeling the jejunal BBM vesicles (Tables I and II), in the same manner as perturbation was indicated in colonic BBM (2). The increase in membrane permeability due to membrane perturbation was confirmed by the increase in CF released from the BBM vesicles by C10 (Table III). This enhancing mechanism was very similar to that reported previously in the colon (2); however, the effect of C10 on the release of CF from the BBM vesicles was greater in the jejunum than the colon (Table III), indicating some contradiction of the finding that C10 enhancement of colonic cefmetazole absorption is greater than C10 enhancement of jejunal absorption.

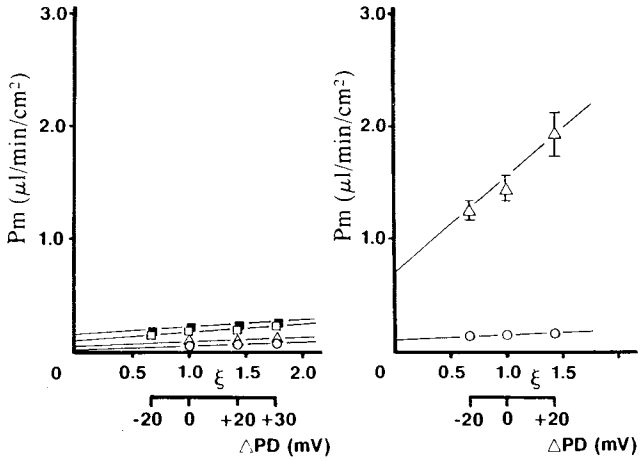

Fig. 6. Effects of applied potential difference (ΔPD) on the permeation clearance (P_m) of cefmetazole in the jejunum of the rat and rabbit (left) and in the colon of the rat (right). (○) Control (in the rat in the absence of enhancer; (△) in the rat in the presence of 0.25% sodium caprate; (□) control in the rabbit; (■) in the rabbit in the presence of 0.25% sodium caprate. Each value represents the mean ± SE of five determinations (more than three animals). For small SE, a bar is included in the symbol. Left: Regression line in the control in the rat—$y = 0.0400x - 0.0039$ ($r = 0.866$, $p < 0.01$); in the rat in the presence of C10—$y = 0.0356x - 0.0251$ ($r = 0.567$, $0.01 < p < 0.05$). No significant correlation was found for the rabbit jejunum. Right: Regression line in the control in the rat—$y = 0.0573x - 0.0737$ ($r = 0.762$, $0.01 < p < 0.05$); in the rat in the presence of 0.25% sodium caprate—$y = 0.841x + 0.708$ ($r = 0.624$, $0.01 < p < 0.05$).

To explain this contradiction, we examined the enhancing effect of C10 on the jejunal paracellular pathway. We have already reported that C10 increased the equivalent pore radius of the colonic membrane (3). The equivalent pore radius is obtained from the ratio of the water filtration rate to the water diffusive permeation rate through the paracellular pathway, assuming that the pathway consists of uniformly circular pores with equal radii (16). Accordingly, this equivalent pore radius is introduced to describe a physical property of a complex biological membrane in operational terms. In this study, to get more practical information about the pore route than the equivalent pore radius, the jejunal membrane permeabilities of water-soluble low-lipophilic nonelectrolytes of various molecular weights were determined, using the Ussing-type chamber technique in the same manner as reported previously for the colon (8). The results shown in Figs. 3 and 4 indicate that the relationship between P_m and D_{fr} is very similar to that found in the colon. Namely, the existence of at least two pore routes was suggested; a large pore route which admitted the free diffusion of all compounds used in this study and a small pore route in which permeation was restricted to compounds of lower molecular weight than erythritol. However, the most important difference between jejunal and colonic permeation was that neither C10 nor C8 had any effect on the jejunal permeability of any of the nonelectrolytes in either the rabbit or the rat ($p > 0.05$ versus the control).

Result showing that C10 has no effect on the jejunal paracellular pathway can also be derived from the impedance analysis of rabbit jejunum. The R_j value shown in Fig. 5 (10–20 Ω · cm^2) is very small in comparison with the value reported by us in the rat colon, 60–70 Ω · cm^2 (10), and with the value of a few hundred ohms per square centimeter reported in the rabbit colon by other workers (17). Accordingly, it can be assumed that the jejunum in the control is originally very leaky and thus it might be impossible to achieve any result with C10. In other words, it may be assumed that there is a limit of leakiness above which an enhancer cannot loosen the tight junction in the paracellular pathway.

Further, the relationship between P_m and ΔPD, determined by the voltage clamp technique, showed remarkable differences in different absorption sites (Fig. 6). In the rat

colon, C10 increased both the transcellular and the paracellular permeability of cefmetazole to about 10 times and 15 times, respectively, those of the control. In the jejunum, a C10 effect on the transcellular permeability of cefmetazole was expected from the increase in CF permeability caused by BBM perturbation (Tables I–III); however, no effect on the P_m of cefmetazole was found (Fig. 6). The reason is still unclear, but it might be due partly to the low detection capability of the voltage clamp technique. The usefulness of the voltage clamp technique is that it separates total membrane permeability into paracellular and transcellular permeability. Evaluation of transcellular permeability is based on the intercept of the linear relationship of P_m vs ξ; however, in the case of the poor jejunal absorption of cefmetazole, which was not very much increased even in the presence of C10, the interindividual variation of P_m may render this evaluation obscure. Accordingly, in this study, we found this technique to be useful largely for determining C10 enhancement of colonic cefmetazole absorption. The significant decrease in potential difference, short circuit, and electric resistance which is induced by C10 and C8 was found just in the colon, and not in the jejunum (data not shown). These results suggest that the effect of enhancers on the transcellular active transport and the paracellular passive transport is minor in the jejunum.

Absorption site differences in the C10 effect also suggest that C10 enhancement of drug absorption is not due to membrane damage caused by its surface-active effects. If the surface-active effect were a main factor, the above site-specific C10 effect should not have been found in the nonelectrolyte permeability and impedance analysis. The C10 effect can be related to reversible membrane alteration, since C10-induced changes of R_j and C_M returned to their respective control levels after the removal of C10 (10).

In summary, jejunal cefmetazole absorption was increased significantly by C10, but to a smaller extent than colonic absorption. Membrane perturbation caused by the interaction between C10 and membrane proteins or lipids is proposed as the main enhancing mechanism of the transcellular permeability of water-soluble compounds. It is concluded that the sensitivity of the paracellular pathway to an enhancer explains the greater enhancing effect of C10 on the colonic permeability of cefmetazole than on its jejunal permeability.

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