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Studies on the Promoting Effects of Carboxylic Acid Derivatives on the Rectal Absorption of β-Lactam Antibiotics in Rats[1)]

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The promoting effects of sodium salts of *N*-acyl-L-phenylalanines, *p*-substituted benzoic acids, saturated straight-chain fatty acids, saturated straight-chain α-bromofatty acids and *N*-acyl-*N*-methylglycines on the rectal absorption of sodium ampicillin (ABPC Na) were investigated in rats. The absorption-promoting effect of each carboxylic acid sodium salt was found to be parabolically correlated with its lipo-hydrophilic character (log *P*). The optimal log *P* value (log P_0) of carboxylic acids exerting the maximum rectal absorption-promoting effect was in the range of 4.2—4.8.

Among these carboxylic acids, sodium caprate was selected for examination of its rectal absorption-promoting action on four penicillins (ampicillin, sulbenicillin, piperacillin and mezlocillin) and eight cephalosporins (cephacetrile, ceftizoxime, cephalothin, cefazolin, cefmetazole, cefotiam, cefoperazone and cefpiramide). The extents of rectal absorption of the β-lactam antibiotics coadministered with sodium caprate were found to correlate well with the permeability of the drugs to cellulose membrane.

Keywords——rectal absorption; absorption-promoting effect; cellulose membrane permeability; β-lactam antibiotics; *N*-acyl-L-phenylalanine; *p*-substituted benzoic acid; fatty acid; α-bromofatty acid; *N*-acyl-*N*-methylglycine

Absorption of many drugs from the rectum as well as the intestinal tract is well known to depend mainly on their ionization state and lipid–water partition characteristics.[2—6)] β-Lactam antibiotics in general are poorly absorbed from the rectum, probably because they have a relatively acidic carboxyl group in the nucleus and, in addition, are very hydrophilic molecules.

Many attempts have been made to enhance the rectal absorption of hydrophilic drugs including β-lactam antibiotics by combination with an absorption promoter. Enamine derivatives of amino acids,[7—9)] surfactants,[10—12)] sodium salts of fatty acids,[13,14)] anti-inflammatory agents[15,16)] and salicylate and its derivatives[17,18)] have been reported to act as absorption promoters.

In this study, we investigated the absorption-promoting effects of sodium salts of various carboxylic acids on sodium ampicillin (ABPC Na), which is extensively used as a broad-spectrum penicillin, and examined the relationship between the physico-chemical properties and absorption-promoting effects of the salts.

The study also included an examination of the rectal absorption-promoting effects of sodium caprate, one of the carboxylic acid sodium salts found to have satisfactory absorption-promoting effects, on various β-lactam antibiotics and an investigation into the relationship between the physico-chemical properties of β-lactam antibiotics and the promoting effects of sodium caprate on the rectal absorption of the antibiotics.

Experimental

Materials——Sodium capronate, sodium caprylate, sodium caprate, sodium laurate, sodium myristate, sodium palmitate and sodium benzoate were obtained from Tokyo Kasei Kogyo Co., Ltd. *p*-Acetaminobenzoic acid, *p*-*n*-butoxybenzoic acid, *p*-*n*-butylbenzoic acid, *p*-*n*-pentylbenzoic acid and *p*-*n*-octylbenzoic acid were purchased from Tokyo Kasei Kogyo Co., Ltd. and used as the sodium salts. *N*-Acyl-L-phenylalanines and *N*-acyl-*N*-methylglycines were prepared from L-phenylalanine (Wako Pure Chemicals Co., Ltd.), and *N*-methylglycine (sarcosine, Tokyo Kasei Kogyo Co., Ltd.), respectively, by the method of Tsubone[19] and used as the sodium salts. α-Bromofatty acids were synthesized from fatty acids (Tokyo Kasei Kogyo Co., Ltd.) in the manner described by Clarke[20] and used as the sodium salts. Samples of sodium ampicillin (ABPC Na: Toyojozo Co.), sulbenicillin (SBPC: Takeda Chemical Industries.), piperacillin (PIPC: Toyama Chemical Co.), mezlocillin (MZPC: Takeda Chemical Industries.), cephacetrile (CEC: Takeda Chemical Industries.), ceftizoxime (CZX: Fujisawa Pharmaceutical Co.), cephalothin (CET: Shionogi & Co.), cefazolin (CEZ: Fujisawa Pharmaceutical Co.), cefmetazole (CMZ: Sankyo Co.), cefotiam (CTM: Takeda Chemical Industries) and cefoperazone (CPZ: Toyama Chemical Co.) were used as supplied. Cefpiramide (CPM) was synthesized in the research laboratories of Kyoto Pharmaceutical Industries in a manner similar to that described by Izaka *et al.*[21] Witepsol H-5 (Dynamit Nobel Chemicals, Troisdorf-Oberlat, West Germany) was used as a suppository base.

Preparation of Suppositories——(i) Suppositories for the Experiment on the Effect of Carboxylic Acid Sodium Salts on the Rectal Absorption of ABPC Na: Suppositories were prepared by the fusion method. Four hundred μmol of carboxylic acid sodium salt and 250 mg (potency) of ABPC Na were mixed with an adequate amount of suppository base to give 1500 mg of molten mass. The molten mass thus obtained was poured into metal molds to obtain suppositories, which contained a dose of ABPC of 12.5 mg/kg.

(ii) Suppositories for the Experiment on the Promoting Effect of Sodium Caprate on Rectal Absorption of Various β-Lactam Antibiotics: Suppositories were prepared in a manner similar to that described above. The molten mass was prepared so as to contain 62.5 mg of sodium caprate and 250 mg (potency) of antibiotic per 1250 mg, and was poured into metal molds to give suppositories containing a dose of antibiotic of 12.5 mg/kg.

***In Vivo* Absorption Study**——Male Wistar rats weighing 170—230 g were used. Before the experiment, the animals were starved overnight but were given water freely. A test suppository was administered rectally at an antibiotic dose of 12.5 or 25.0 mg/kg, then the anus was sealed with a adhesive for surgical use (Aron Alpha®) to prevent leakage of rectal contents during the experiment. The antibiotics for injection were dissolved in distilled water. The drugs were administered intramuscularly or intravenously, at a dose of 12.5 or 25.0 mg/kg, respectively. Blood samples were collected from the jugular vein at the designated intervals after administration.

Cellulose Membrane Permeability——Visking cellulose tubing, 30/32 inches in diameter, was used as cellulose membrane. The tubing was first boiled in water three times for half an hour with thorough rinsing each time. The dialysis bags prepared from the tubing were filled with 3 ml of 1/15 M phosphate buffer solution (pH 7.0) containing 20 mM β-lactam antibiotic, and they were bathed in 150 ml of 1/15 M phosphate buffer solution (pH 7.0) maintained at 20 °C. The external solution was continuously stirred. Aliquots of the external solution were pipetted out at suitable intervals and the concentration of antibiotic was determined. The elimination rate constants calculated on the basis of the decrease of antibiotic in the dialysis bag were used as the cellulose membrane permeability rate constants (*K*).

TABLE I. Analytical Conditions for HPLC in the Determination of β-Lactam Antibiotics

Antibiotics	Mobile phase 0.035 M NH_4Cl : MeOH	Detector
ABPC	7 : 3	UV 225 nm
SBPC	7 : 3	UV 230 nm
PIPC	3 : 2	UV 254 nm
MZPC	1 : 1	UV 230 nm
CEC	4 : 1	UV 260 nm
CZX	9 : 1	UV 254 nm
CET	3 : 2	UV 240 nm
CEZ	7 : 3	UV 270 nm
CMZ	4 : 1	UV 270 nm
CTM	7 : 3	UV 260 nm
CPZ	7 : 3	UV 260 nm

Instrument: JASCO TRIROTAR, flow rate 2.0 ml/min.

Analytical Methods——Antibiotic concentrations in blood were determined by the agar diffusion cup plate method with the test strains *Micrococcus luteus* ATCC 9341 for ABPC, PIPC and CPZ, *Bacillus subtilis* ATCC 6633 for SBPC, MZPC, CEC, CZX, CET, CEZ, CMZ and CTM, and *Escherichia coli* NIHJ for CPM.

For the examination of the cellulose membrane permeability, antibiotic concentrations in the external solution were assayed by a high-performance liquid chromatographic method (HPLC). A reversed-phase column (Lichrosorb RP-8) with a 0.035 M NH_4Cl–methanol mixture as the mobile phase was employed. Analytical conditions for HPLC are listed in Table I.

Partition Coefficient——The partition coefficients of sodium *N*-butyryl-L-phenylalaninate, sodium benzoate, sodium capronate and sodium *N*-hexanoyl-*N*-methylglycinate, which were selected as typical compounds of each series of carboxylic acids, were measured as mentioned below.

A carboxylic acid sodium salt was dissolved in 0.5 N HCl saturated with *n*-octanol at a concentration of 1 mM. Ten ml of the solution was put into a test tube containing 10 ml of *n*-octanol saturated with 0.5 N HCl. The test tube was shaken vigorously at 25 °C. When equilibrium had been achieved, the aqueous layer was separated by centrifugation, and the concentrations of *N*-butyryl-L-phenylalanine and benzoic acid in the aqueous layer were measured by ultraviolet (UV) spectrometry (254 nm). On the other hand, the concentrations of caproic acid of *N*-hexanoyl-*N*-methylglycine were measured by fluorometry following the method of Nimura *et al.*[22] using anthryldiazomethane (ADAM) as a fluorescent reagent. The fluorescence was measured at 412 nm, with excitation at 365 nm.

The partition coefficients of other carboxylic acids were calculated on the basis of the observed values of each series of carboxylic acids, by using the method of Hansch and Fujita,[23,24] taking advantage of the additivity of π values.

Results

Effects of Carboxylic Acid Sodium Salts on the Rectal Absorption of ABPC

ABPC Na was administered intramuscularly or rectally to rats at the dose of 12.5 mg/kg for examination of its absorption. As shown in Fig. 1, absorption of ABPC Na itself through the rectum was poor, and the relative bioavailability, expressed as the ratio of the area under the curve in plasma (*AUC*) after rectal and intramuscular administration, was as low as 10.6%.

Then, the rectal administration of the mixture of ABPC Na (12.5 mg/kg) with each of the

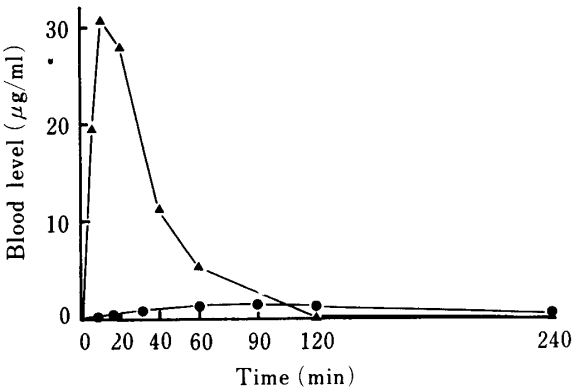


Fig. 1. Blood Levels of ABPC after Intramuscular and Rectal Administration (12.5 mg/kg) to Rats

—▲—, *i.m.*; —●—, rectal (without carboxylic acids).
Each point represents the mean of 3 animals.

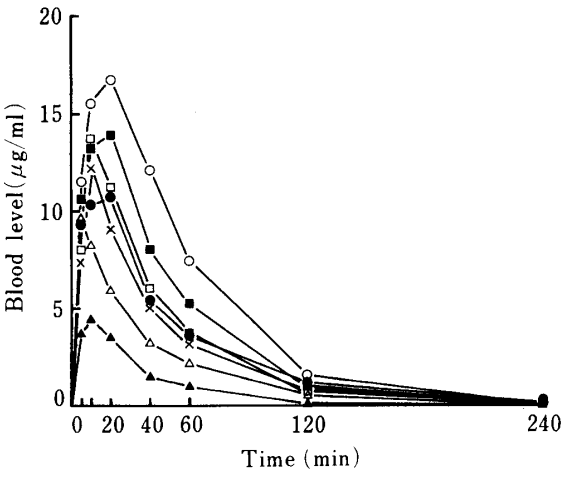
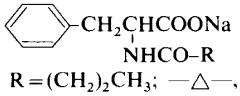
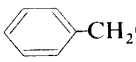
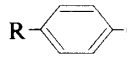
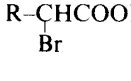
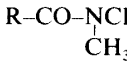


Fig. 2. Effect of *N*-Acyl-L-phenylalanine Sodium Salts on Rectal Absorption of ABPC (12.5 mg/kg) in Rats



—▲—, $R=(CH_2)_2CH_3$; —△—, $R=(CH_2)_4CH_3$; —●—, $R=(CH_2)_6CH_3$; —○—, $R=(CH_2)_8CH_3$; —■—, $R=(CH_2)_{10}CH_3$; —□—, $R=(CH_2)_{12}CH_3$; —×—, $R=(CH_2)_{14}CH_3$.
Each point represents the mean of 3 animals.

TABLE II. Structures of Carboxylic Acid Sodium Salts

Structure	R	Name	Compd. No.
N-Acyl-L-phenylalanine sodium salts			
	$-(CH_2)_2CH_3$	Sodium *N*-butyryl-L-phenylalaninate	Ia
	$-(CH_2)_4CH_3$	Sodium *N*-hexanoyl-L-phenylalaninate	Ib
	$-(CH_2)_6CH_3$	Sodium *N*-octanoyl-L-phenylalaninate	Ic
	$-(CH_2)_8CH_3$	Sodium *N*-decanoyl-L-phenylalaninate	Id
	$-(CH_2)_{10}CH_3$	Sodium *N*-lauroyl-L-phenylalaninate	Ie
	$-(CH_2)_{12}CH_3$	Sodium *N*-myristoyl-L-phenylalaninate	If
	$-(CH_2)_{14}CH_3$	Sodium *N*-palmitoyl-L-phenylalaninate	Ig
p-Substituted benzoic acid sodium salts			
	$-NHCOCH_3$	Sodium *p*-acetoaminobenzoate	IIa
	$-H$	Sodium benzoate	IIb
	$-O(CH_2)_3CH_3$	Sodium *p*-*n*-butoxybenzoate	IIc
	$-(CH_2)_3CH_3$	Sodium *p*-*n*-butylbenzoate	IId
	$-(CH_2)_4CH_3$	Sodium *p*-*n*-pentylbenzoate	IIe
	$-(CH_2)_7CH_3$	Sodium *p*-*n*-octylbenzoate	IIf
Fatty acid sodium salts			
	$-(CH_2)_4CH_3$	Sodium capronate	IIIa
	$-(CH_2)_6CH_3$	Sodium caprylate	IIIb
	$-(CH_2)_8CH_3$	Sodium caprate	IIIc
	$-(CH_2)_{10}CH_3$	Sodium laurate	IIId
	$-(CH_2)_{12}CH_3$	Sodium myristate	IIIe
	$-(CH_2)_{14}CH_3$	Sodium palmitate	IIIf
α-Bromofatty acid sodium salts			
	$-(CH_2)_3CH_3$	Sodium α-bromocapronate	IVa
	$-(CH_2)_5CH_3$	Sodium α-bromocaprylate	IVb
	$-(CH_2)_7CH_3$	Sodium α-bromocaprate	IVc
	$-(CH_2)_9CH_3$	Sodium α-bromolaurate	IVd
	$-(CH_2)_{11}CH_3$	Sodium α-bromomyristate	IVe
	$-(CH_2)_{13}CH_3$	Sodium α-bromopalmitate	IVf
N-Acyl-*N*-methylglycine sodium salts			
	$-(CH_2)_4CH_3$	Sodium *N*-hexanoyl-*N*-methylglycinate	Va
	$-(CH_2)_6CH_3$	Sodium *N*-octanoyl-*N*-methylglycinate	Vb
	$-(CH_2)_8CH_3$	Sodium *N*-decanoyl-*N*-methylglycinate	Vc
	$-(CH_2)_{10}CH_3$	Sodium *N*-lauroyl-*N*-methylglycinate	Vd
	$-(CH_2)_{12}CH_3$	Sodium *N*-myristoyl-*N*-methylglycinate	Ve
	$-(CH_2)_{14}CH_3$	Sodium *N*-palmitoyl-*N*-methylglycinate	Vf

five series of carboxylic acids (20 μmol/kg) in Table II as a suppository was studied in an attempt to improve absorption of ABPC Na from the rectum.

The results are presented in Figs. 2—6 and Table III. These results indicated that the five series of carboxylic acids all significantly improved the absorption of ABPC Na from the rectum. The maximum plasma concentration (C_{max}) and AUC of ABPC after rectal administration of the mixture was initially enhanced with lengthening of the alkyl side-chain of the coadministered carboxylic acids, but decreased with further lengthening of the alkyl side-chain (Table III). Thus, there was an optimal length of the alkyl side-chain for the absorption-promoting effect. The best absorption-promoting effects were exhibited by sodium *N*-decanoyl-L-phenylalaninate, sodium *p*-*n*-pentylbenzoate, sodium caprate, sodium α-bromocaprate and sodium *N*-lauroyl-*N*-methylglycinate among each series of carboxylic acids, the bioavailabilities being 93.5, 75.9, 62.8, 56.3 and 53.8%, respectively.

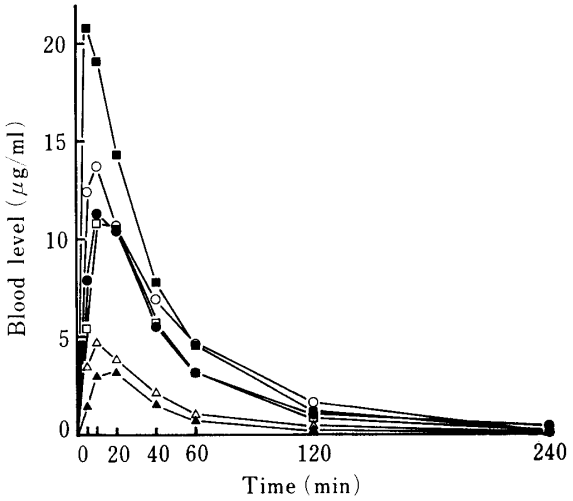
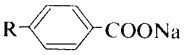


Fig. 3. Effect of *p*-Substituted Benzoic Acid Sodium Salts on Rectal Absorption of ABPC (12.5 mg/kg) in Rats



▲, R=NHCOCH$_3$; △, R=H; ●, R=O(CH$_2$)$_3$CH$_3$; —○—, R=(CH$_2$)$_3$CH$_3$; —■—, R=(CH$_2$)$_4$CH$_3$; —□—, R=(CH$_2$)$_7$CH$_3$.
Each point represents the mean of 3 animals.

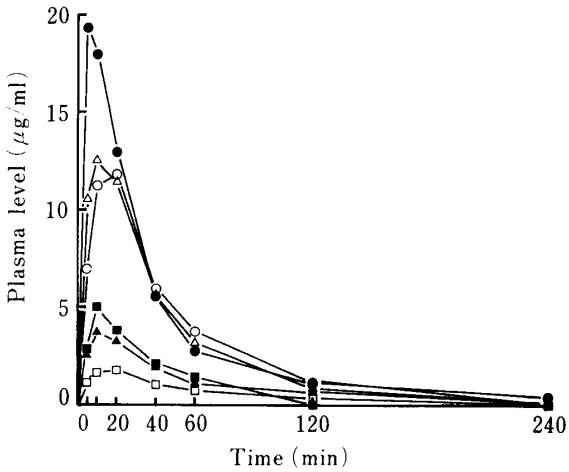


Fig. 4. Effect of Fatty Acid Sodium Salts on Rectal Absorption of ABPC (12.5 mg/kg) in Rats

—▲—, R=(CH$_2$)$_4$CH$_3$; —△—, R=(CH$_2$)$_6$CH$_3$; —●—, R=(CH$_2$)$_8$CH$_3$; —○—, R=(CH$_2$)$_{10}$CH$_3$; —■—, R=(CH$_2$)$_{12}$CH$_3$; —□—, R=(CH$_2$)$_{14}$CH$_3$.
Each point represents the mean of 3 animals.

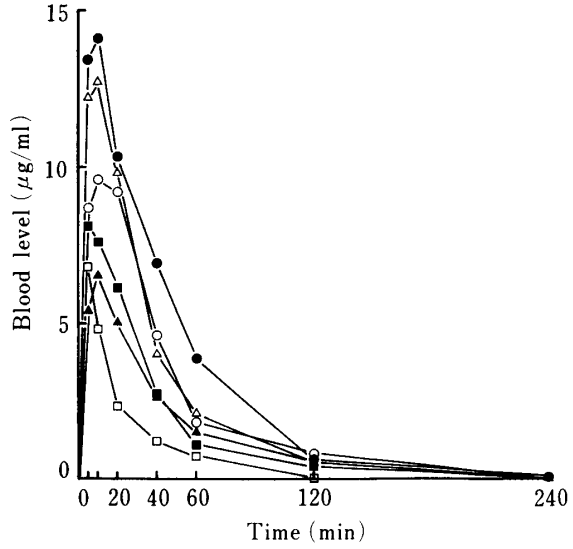
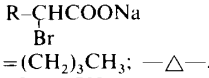


Fig. 5. Effect of α-Bromofatty Acid Sodium Salts on Rectal Absorption of ABPC (12.5 mg/kg) in Rats



—▲—, R=(CH$_2$)$_3$CH$_3$; —△—, R=(CH$_2$)$_5$CH$_3$; —●—, R=(CH$_2$)$_7$CH$_3$; —○—, R=(CH$_2$)$_9$CH$_3$; —■—, R=(CH$_2$)$_{11}$CH$_3$; —□—, R=(CH$_2$)$_{13}$CH$_3$.
Each point represents the mean of 3 animals.

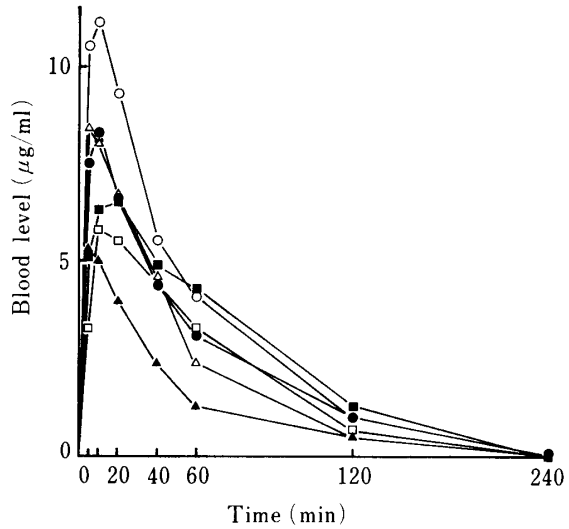
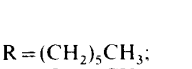


Fig. 6. Effect of *N*-Acyl-*N*-methylglycine Sodium Salts on Rectal Absorption of ABPC (12.5 mg/kg) in Rats



—▲—, R=(CH$_2$)$_4$CH$_3$; —△—, R=(CH$_2$)$_6$CH$_3$; —●—, R=(CH$_2$)$_8$CH$_3$; —○—, R=(CH$_2$)$_{10}$CH$_3$; —■—, R=(CH$_2$)$_{12}$CH$_3$; —□—, R=(CH$_2$)$_{14}$CH$_3$.
Each point represents the mean of 3 animals.

Next, the relationship between the partition coefficient (log *P*) in the *n*-octanol–water system and the rectal absorption-promoting effect on ABPC Na was studied. A plot of the log *P* value of each of the carboxylic acids against the logarithm of relative bioavailability resulted in a parabolic relation in convex form (Fig. 7). When this relation was expressed by a quadratic equation by the least-squares method, a satisfactory correlation was obtained as

TABLE III. Effect of Carboxylic Acids on the Rectal Absorption of ABPC

Compd. group.	Compd. No.	log P_{oct}	ABPC		
			C_{max} (μg/ml)	AUC (μg·h/ml)	Bio.[a]
N-Acyl-L-phenylalanine sodium salts	Ia	1.11	4.4±1.3	3.2±0.5	16.1
	Ib	2.11	9.6±0.7	6.6±1.5	33.2
	Ic	3.11	10.7±1.3	11.1±0.5	55.8
	Id	4.11	16.7±2.2	18.6±1.4	93.5
	Ie	5.11	13.9±1.2	13.9±0.5	69.8
	If	6.11	13.7±3.5	10.6±2.4	53.3
	Ig	7.11	12.2±3.4	9.6±1.9	48.2
p-Substituted benzoic acid sodium salts	IIa	0.91	3.1±0.9	2.5±0.8	12.6
	IIb	1.88	4.7±1.9	3.8±1.0	19.1
	IIc	3.48	11.3±2.4	10.4±1.4	52.3
	IId	3.88	13.7±2.6	11.9±2.3	59.8
	IIe	4.38	20.8±2.6	15.1±1.6	75.9
	IIf	5.88	10.8±1.7	9.9±2.1	49.7
Fatty acid sodium salts	IIIa	2.09	3.7±0.8	4.0±0.8	20.1
	IIIb	3.09	12.5±0.9	10.1±1.0	50.8
	IIIc	4.09	19.3±3.1	12.5±1.9	62.8
	IIId	5.09	11.8±2.1	11.0±1.2	55.3
	IIIe	6.09	5.0±0.6	3.5±0.6	17.6
	IIIf	7.09	1.7±0.2	2.0±0.4	10.1
α-Bromofatty acid sodium salts	IVa	2.33	6.5±1.4	4.9±0.4	24.6
	IVb	3.33	12.7±2.4	8.4±1.7	42.2
	IVc	4.33	14.1±2.3	11.2±1.5	56.3
	IVd	5.33	9.6±1.2	8.0±1.0	40.2
	IVe	6.33	8.1±0.6	5.3±0.7	26.6
	IVf	7.33	6.8±2.1	2.6±0.6	13.1
N-Acyl-*N*-methylglycine sodium salts	Va	1.14	5.3±1.4	4.4±1.4	22.1
	Vb	2.14	8.4±2.4	7.3±1.4	36.7
	Vc	3.14	8.3±1.2	8.4±1.3	42.2
	Vd	4.14	11.1±2.2	10.7±0.6	53.8
	Ve	5.14	6.5±1.1	9.3±1.0	46.7
	Vf	6.14	5.8±1.3	7.3±0.8	36.7
Control (without promoter)			2.4±0.4	2.1±0.7	10.6

Dose, ABPC Na 12.5 mg/kg; carboxylic acid derivatives 20 μmol/kg.
a) Bioavailability was calculated as AUC after rectal/AUC after *i.m.* administration.
Each value represents the mean ± S.E. of 3 rats.

shown in Eqs. (1)—(5), where n, r and $\log P_0$ indicate the number of compounds studied, the correlation coefficient and the optimal $\log P$ value, respectively.

N-Acyl-L-phenylalanines

$$\log \text{bioavailability} = -0.050(\log P)^2 + 0.481 \log P + 0.742 \quad (n=7,\ r=0.969,\ \log P_0 = 4.8) \tag{1}$$

p-Substituted benzoic acids

$$\log \text{bioavailability} = -0.053(\log P)^2 + 0.502 \log P + 0.628 \quad (n=7,\ r=0.977,\ \log P_0 = 4.7) \tag{2}$$

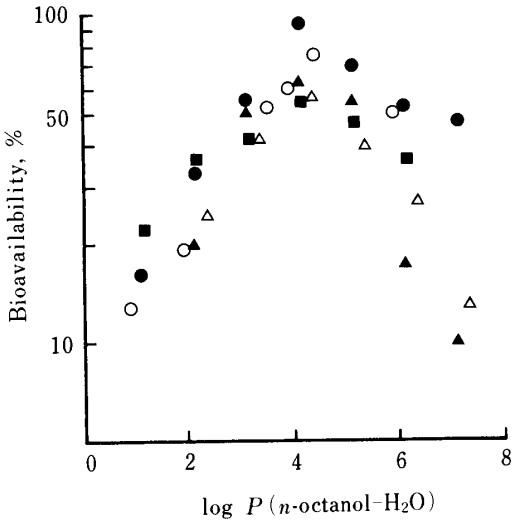


Fig. 7. Relationship between Bioavailability Following Rectal Administration of ABPC with Carboxylic Acid Derivatives and Octanol–Water Partitioning Properties (log P)

N-Acyl-L-phenylalanine sodium salts (●), *p*-substituted benzoic acid sodium salts (○), fatty acid sodium salts (▲), α-bromofatty acid sodium salts (△), *N*-acyl-*N*-methylglycine sodium salts (■).

Fatty acids

$$\log \text{bioavailability} = -0.100(\log P)^2 + 0.830 \log P + 0.043 \quad (n=6,\ r=0.962,\ \log P_0 = 4.2) \tag{3}$$

α-Bromofatty acids

$$\log \text{bioavailability} = -0.070(\log P)^2 + 0.617 \log P + 0.346 \quad (n=6,\ r=0.991,\ \log P_0 = 4.4) \tag{4}$$

N-Acyl-*N*-methylglycines

$$\log \text{bioavailability} = -0.038(\log P)^2 + 0.318 \log P + 1.035 \quad (n=6,\ r=0.986,\ \log P_0 = 4.2) \tag{5}$$

These equations indicate that the optimal log P value ($\log P_0$) of the carboxylic acids exerting the maximum rectal absorption-promoting effect is in the range of 4.2—4.8.

Rectal Absorption-Promoting Effects of Sodium Caprate on Various β-Lactam Antibiotics

Among the sodium salts of carboxylic acids exhibiting a satisfactory rectal absorption-promoting effect on ABPC Na, sodium caprate, a natural fatty acid, was chosen for examination of its rectal absorption-promoting effect on various penicillins and cephalosporins. A suppository containing one of these β-lactam antibiotics and sodium caprate was administered rectally to rats at the dose of 25.0 mg/kg as β-lactam antibiotic. Then, the blood concentration was determined to obtain the AUC, and its ratio to AUC after intravenous administration was used for calculation of the bioavailability as an indicator of the extent of rectal absorption. The results are shown in Table IV. Most of the β-lactam antibiotics shown in this report are absorbed poorly from the rectum when they are administered without sodium caprate (bioavailability $< 10\%$), but there was a remarkable improvement in absorption in the presence of sodium caprate. However, the extent of improvement differed considerably from one type of drug to another.

In order to clarify these differences, the relationship between the molecular weight (MW) of β-lactam antibiotics and the bioavailability when the drugs were administered rectally as a suppository containing sodium caprate was examined. As shown in Fig. 8, the coefficient of correlation between them was 0.611, a relatively poor correlation.

Next, we measured the permeability of each β-lactam antibiotic to cellulose membrane, as a model of the vital membrane. The results are presented in Table V. When the cellulose membrane permeation rate constant (K) of each of the β-lactam antibiotics was plotted

TABLE IV. Promoting Effect of Sodium Caprate on the Rectal Absorption of β-Lactam Antibiotics

Drugs	C_{max} Rectal	AUC (μg·h/ml)		Bioavailability (%)
		Rectal	*i.v.*	
Penicillins				
ABPC	19.6±3.1	32.8±5.1	46.0± 3.3	71.3
SBPC	5.3±2.1	4.9±1.1	12.0± 1.7	40.8
PIPC	10.6±0.8	7.0±0.4	10.9± 0.4	64.2
MZPC	5.7±0.3	3.4±0.1	10.0± 1.6	34.0
Cephalosporins				
CEC	29.7±1.2	75.9±5.9	94.3± 7.7	80.5
CZX	24.5±2.6	26.7±4.6	43.1± 4.1	61.9
CET	27.6±6.9	23.4±5.8	53.7±13.8	43.6
CEZ	23.3±3.4	60.4±8.6	65.4± 7.0	92.4
CMZ	9.1±0.4	10.5±0.9	14.4± 0.4	72.9
CTM	15.9±1.5	12.3±1.1	20.3± 1.1	60.6
CPM	7.1±2.8	5.9±0.4	22.5± 1.4	26.2
CPZ	10.1±0.5	5.7±1.1	20.7± 1.0	27.5

Dose, β-lactam antibiotics 25.0 mg/kg; sodium caprate 6.25 mg/kg.
C_{max}, peak level of β-lactam antibiotics.
Bioavailability was calculated as AUC after rectal/AUC after *i.v.* administration.
Each value represents the mean±S.E. of 3 rats.

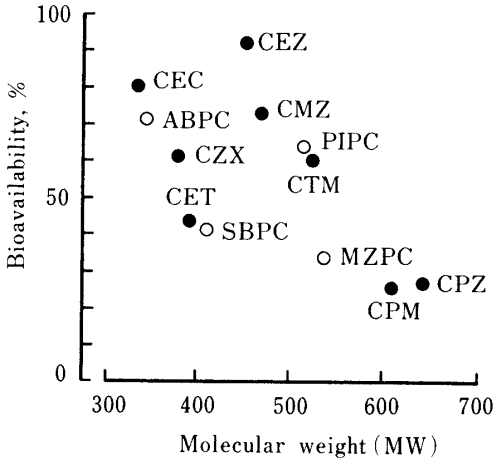


Fig. 8. Relationship between Bioavailability Following Rectal Administration of Drug with Sodium Caprate and Molecular Weight of β-Lactam Antibiotics

○, penicillins; ●, cephalosporins.

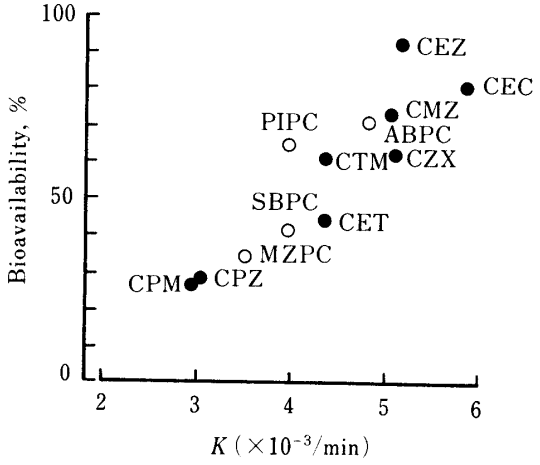


Fig. 9. Relationship between Bioavailability Following Rectal Administration of Drug with Sodium Caprate and Permeability of β-Lactam Antibiotics to Cellulose Membrane

○, penicillins; ●, cephalosporins; K, permeability rate constant.

against the bioavailability of rectally administered suppositories containing the antibiotics and sodium caprate, a satisfactory correlation was noted, with a high correlation coefficient of 0.892 (Fig. 9).

Discussion

It has recently been reported that carboxylic acids having metal-chelating ability improve the rectal absorption of poorly absorbed drugs, including β-lactam antibiotics.[25,26] As a

TABLE V. Permeability of β-Lactam Antibiotics to Cellulose Membrane

Drugs	Molecular weight (as free form)	K ($\times 10^{-3}$/min)	$t_{1/2}$ (min)
Penicillins			
ABPC	349.4	4.812	61.3
SBPC	414.5	3.943	74.0
PIPC	517.5	3.946	77.4
MZPC	539.6	3.511	85.7
Cephalosporins			
CEC	339.3	5.843	50.1
CZX	383.4	5.088	59.6
CET	396.4	4.338	64.7
CEZ	454.5	5.164	53.9
CMZ	471.6	5.054	56.2
CTM	525.6	4.345	66.6
CPM	612.6	2.935	107.6
CPZ	645.7	3.008	102.7

K, permeation rate constant.
$t_{1/2}$, half-life of disappearance from cellulose tubing.
Each value represents the mean for 2 experiments.

possible mechanism, it was suggested that carboxylic acids serve to make the intercellular space more accessible by temporarily eliminating Ca ions of the rectal mucosa; these ions are essential to maintain a tight structure.

In the present study, we examined the absorption-promoting efficacies of five series of carboxylic acids on the rectal absorption of β-lactam antibiotics in terms of the relationship between physico-chemical properties and promoting efficacy. It was found that all of the carboxylic acid sodium salts tested showed an absorption-promoting effect and the compounds with a log P value in the range of 4.2—4.8 had the best efficacy (Fig. 7). It is noteworthy that these values are substantially in agreement with the optimal log P value of 4.19 that Lien *et al.*[27] obtained for acidic drugs in their analysis of the absorption of organic electrolytes based on the buccal absorption data of Beckett *et al.*[28-31]

Among these carboxylic acid sodium salts, sodium caprate was selected for examination of its absorption-promoting effects on various β-lactam antibiotics. Although the extent of rectal absorption of antibiotics given in combination with sodium caprate did not show a satisfactory correlation with molecular weight, it did show a good correlation with cellulose membrane permeability to the drugs (Fig. 9). Nakagaki *et al.*[32,33] reported that the cellulose membrane permeability to compounds frequently correlated well with the apparent molecular weight of the compounds in solution, rather than the true molecular weight. This suggests that the cellulose membrane permeability behavior could be an indicator of apparent molecular size in solution. Therefore, the results shown in Fig. 9 indicate that sodium caprate exhibits a stronger rectal absorption-promoting effect on β-lactam antibiotics with smaller apparent molecular size.

In conclusion, carboxylic acid sodium salts with log P values of 4.2—4.8 exerted the most potent rectal absorption-promoting effect on β-lactam antibiotics, and sodium caprate, one such carboxylic acid sodium salt, showed a stronger promoting efficacy with β-lactam antibiotics having smaller molecular size.

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