Absorption Promoters in the Rectal Absorption of Drugs

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Recently there has been clinical interest in the effects of adjuvants for promoting rectal absorption of poorly absorbed drugs.

Hitherto, salicylate[1], enamine derivatives of amino acid[2] and glyceryl esters of acetoacetic acid[3] were reported as potential absorption promoter.

We have also reported that N-acylcollagen peptide[4], monodesmosides from pericarps of *Sapindus mukurossi*[5], bile salts[6], N-acylamino acids[7] and medium chain length saturated fatty acids[8] improved the rectal absorption of ampicillin(ABPC), cephalothin (CET), cephapirin(CEP), cefazolin(CEZ), phenolsulfonphthalein(PSP) and p-aminobenzoate(PABA) in the rat. Further, we also suggested the contribution of Ca ion chelating ability of the adjuvants in relation to the mechanism of the absorption promoting action[8].

In the present paper, I will show the results obtained in my laboratory from the following two points of view :

1. Efficacies of Some Absorption Promoters
2. A Possible Mechanism of the Promoting Action

1. Efficacies of Some Absorption Promoters

a) N-Acylcollagen Peptide(Cx-CP)

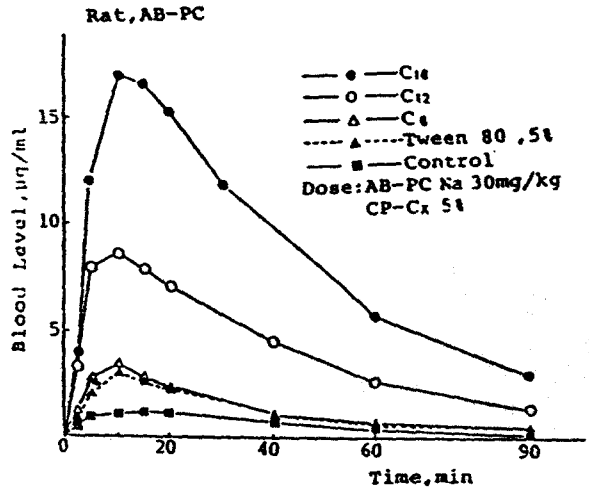
Blood concentrations of ampicillin as a function of time after rectal administration of the suppository containing ABPC and 5% of each of Cx-CP to rats are shown in Fig. 1. Rectal absorption of ABPC from a suppository(base : Witepsol H15) without adjuvants was very low, but a significant increased absorption of ABPC was observed in the presence of each adjuvant.

Fig. 2. shows the effect of C_{18}-CP on the rectal absorption of poorly absorbed atudied. otics from the suppository. Enhanced absorption was observed in all antibiotics sudptie

b) Monodesmosides

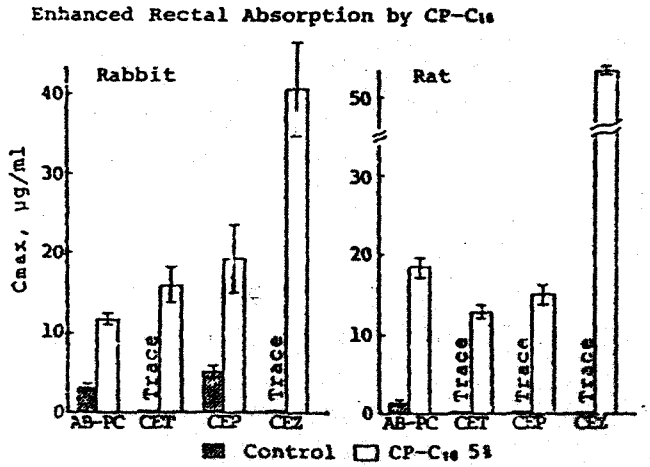
韓亞藥劑學會 秋季學術講演會(1985.11.19 대한약품공업협회)에서 발표되었음

Fig. 1



We initially found that the rectal absorption of ABPC was significantly enhanced by a crude saponin fraction extracted from pericarps of *Sapindus mukurossi* (Enmei-hi). Monodesmosides and bisdesmosides of hederagenin shown in Chart 1 were isolated from this crude drug by Prof. Tanaka and his colleague[3]. Since monodesmosides were sparingly soluble in Tris buffer (pH 7.4, 280 mOsmol/kg), monodesmosides were solubilized with the aid of 0.2% XY-mix. The effect of saponin A on rectal absorption of ABPC from solution injected into rat rectal loop in shown in Fig. 3. After administration of

Fig. 2



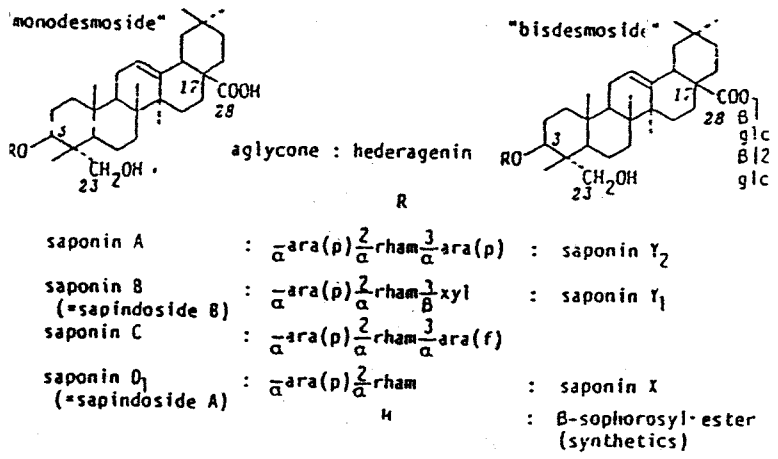
the control solution, which contained ABPC and XY-mix without Saponin A, ABPC was not detected in blood similar to the case of solution containing ABPC alone. This result indicates that the solubilizing agent, XY-mix, has no promoting effect on rectal absorption of ABPC. However, in the presence of Saponin A, the blood concentration of ABPC was significantly increased. The maximum concentration of ABPC in blood (C_{max}) and the area under the concentration-time curve (AUC) after administration with either of three monodesmosides are presented in Fig. 4. All monodesmosides showed comparable promoting effects for the rectal absorption of ABPC. The adjuvant effect of Saponin A on rectal absorption of other antibiotics was examined, with the results in terms of C_{max}, and presented in Fig. 5.

c) Bile Salts

The rectal absorption of ABPC in the presence of various bile salts, such as dehydrocholate(DHC), deoxycholate(DC), taurodeoxycholate(TDC), chenodeoxy cholate(CDC),

Chart 1

Sapindus mukurossi Gaertn. (pericarps) [Sapindaceae]



glycocherodeoxycholate(GCDC), ursodeoxycholate(UDC), cholate(C), taurocholate(TC) and glycocholate(GC), was investigated using the in situ rat rectal loop method. As shown in Fig. 6, a marked but variable absorption promoting effect was observed with dihydroxycholate, whereas trihydroxy and triketo bile salts did not enhance the rectal absorption of ABPC.

d) N-Acylamino Acids

The rectal absorption of ABPC in the presence of N-acylalanine(Cx-A), N-acylphenylalanine(Cx-PA), N-acylglycine(Cx-G) or N-acylphenylglycine(Cx-PG) was inves-

Fig. 3

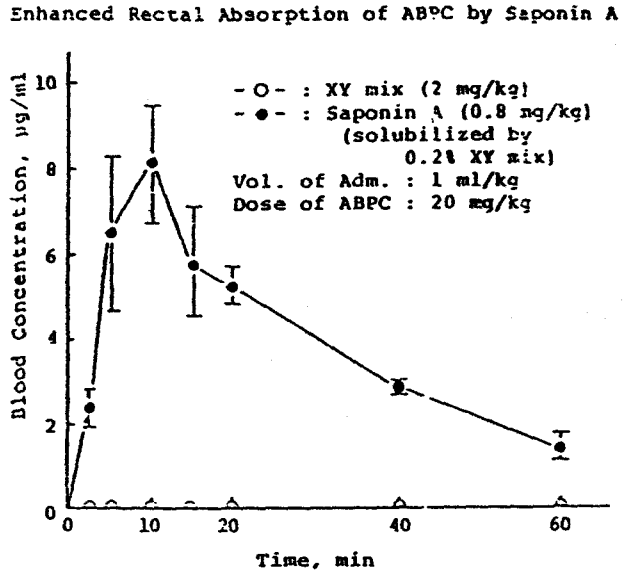

Enhanced Rectal Absorption of ABPC by Saponin A
Blood Concentration, μg/ml
Time, min
-O- : XY mix (2 mg/kg)
-●- : Saponin A (0.8 mg/kg) (solubilized by 0.2% XY mix)
Vol. of Adm. : 1 ml/kg
Dose of ABPC : 20 mg/kg

Fig. 4

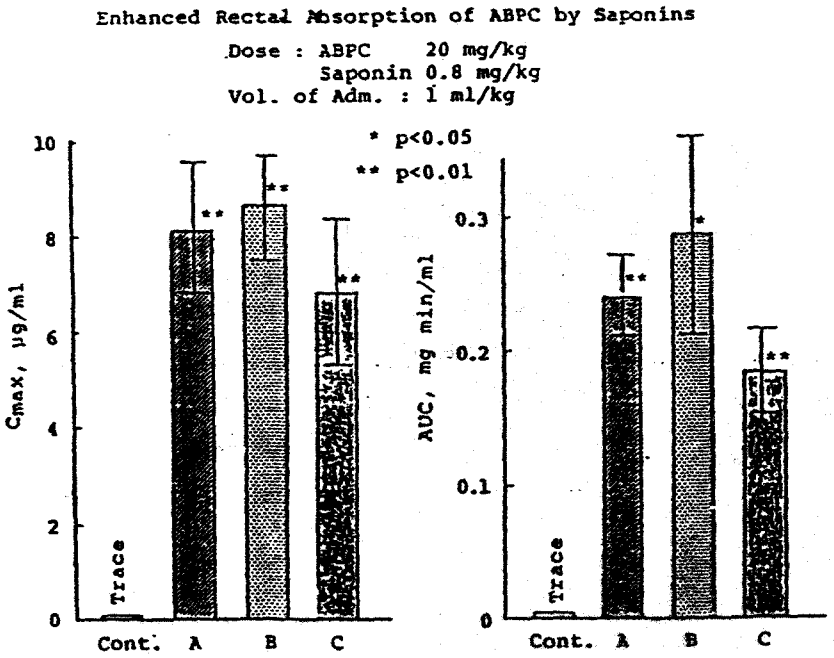

Enhanced Rectal Absorption of ABPC by Saponins
Dose : ABPC 20 mg/kg
Saponin 0.8 mg/kg
Vol. of Adm. : 1 ml/kg
* p<0.05
** p<0.01
Cmax, μg/ml
AUC, mg min/ml
Trace
Cont.
A
B
C

Fig. 5

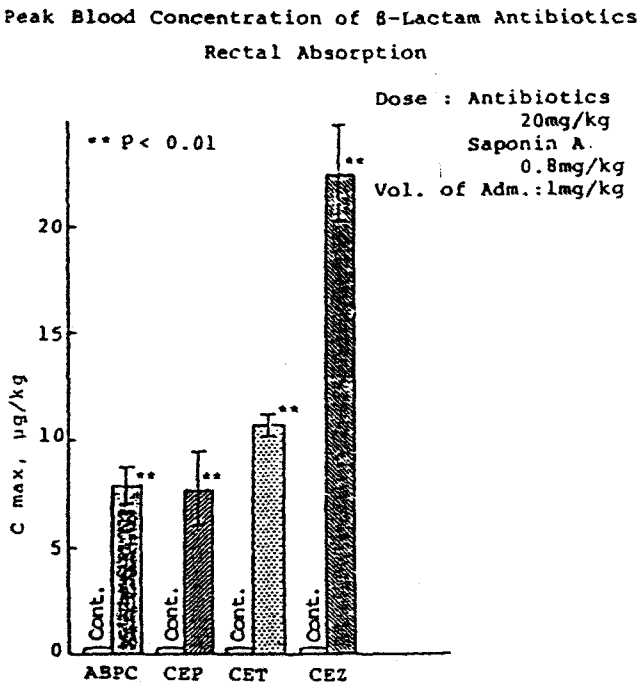

Peak Blood Concentration of β-Lactam Antibiotics
Rectal Absorption
Dose : Antibiotics 20mg/kg
Saponin A. 0.8mg/kg
Vol. of Adm.: 1mg/kg
** P< 0.01
C max, μg/kg
0
5
10
15
20
Cont.
ABPC
CEP
CET
CEZ

Fig. 6

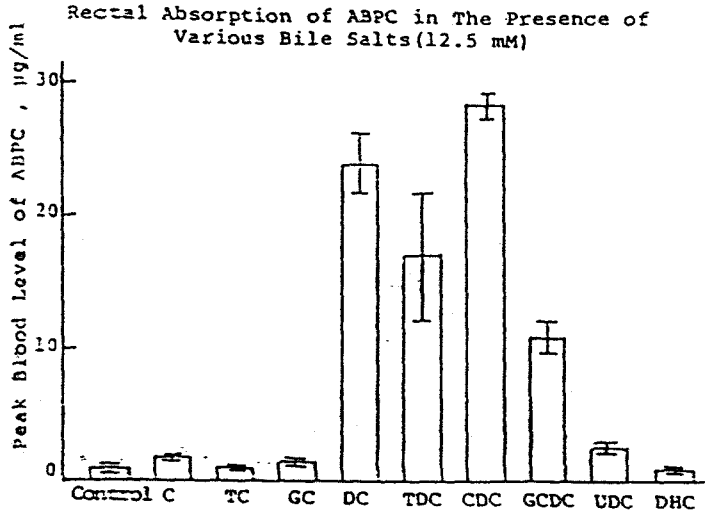
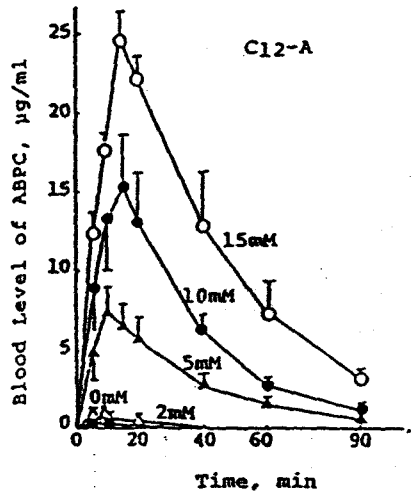

Rectal Absorption of ABPC in The Presence of Various Bile Salts(12.5 mM)
Peak Blood Level of ABPC, μg/ml
0
10
20
30
Control
C
TC
GC
DC
TDC
CDC
GCDC
UDC
DHC

Fig 7

Enhanced rectal absorption of ABPC by C12-A in rats(loop).



tigated using the in situ rat rectal loop method. Fig. 7 shows the results with C_{12}-A. Fig. 8 shows the dose-response curve in absorption promoting effect of Cx-A and Cx-P A. Those of Cx-G and Cx-PG were the identical to those of Cx-A and Cx-PA, respectively.

e) Medium Chain Length Saturated Fatty Acids and Others

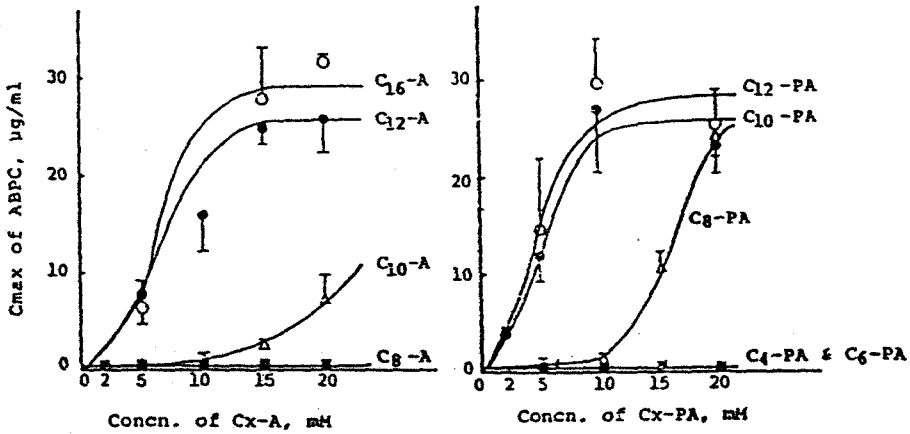
Fig. 9 shows the effect of fatty acids and some acylpeptides on rectal absorption of ABPC in rat rectal loop in terms of C_{max} of ABPC. Caprate(C_{10}), N-myristoyl-L-prolyl-L-prolyl-glycine(M-PPG), N-lauroyl-L-prolyl-L-prolyl-glycine(L-PPG), showed a marked absorption promoting effect.

EDTA has also absorption promoting effect to some extent. The degree of the effect of the adjuvants may depend on the physicochemical nature of poorly absorbed drugs. Fig. 10 shows relations between adjuvants and its effect on the rectal absorption of three different poorly absorbed drugs.

The rectal absorption of ABPC was markedly enhanced by C_{10} or M-PPG. However, the degree of enhanced absorption of PSP and PABA caused by C_{10}, M-PPG and EDTA were almost same. Absorption promoting effect of EDTA for ABPC was almost same as those for PSP and PABA.

These results indicate that C_{10} and M-PPG could be more effective absorption promoter for β-lactam antibiotics than other two adjuvants.

Fig. 8 Effects of the concentration of Cx-A (Cx-PA) on peak blood level of ABPC in rats(loop).



2. A Possible Mechanism of the Promoting Action

Hitherto some mechanisms of the adjuvant effect to promote the rectal absorption of drugs were proposed.

a) reduction of non-protein sulfhydryls in the tissue

b) contribution to solvent drag

c) perturbation of cell membrane

d) Ca ion chelating ability and tissue affinity of the adjuvants

We have investigated the mechanism of the promoting action from a view point of Ca ion chelating ability and tissue affinity of the adjuvants.

Fig. 11 shows the reduction of the enhanced effect of M-PPG with an increase of the concentration of calcium chloride present in the solution administered to the rat rectal loop. Similar phenomena were observed in case of C_{10}.

Since C_{10} is already clinically used as an absorption promoter in the ampicillin suppository which was recently developed in Japan, we tried to explain the difference in the concentration required to get the same absorption promoting effect between C_{10} and C_8.

As an example, the absorption promoting effects of C_{10} on PSP and sodium ampicillin are shown in Fig. 12 and 13. The plasma level of PSP was only 2 $\mu g/ml$ or lower when PSP Na was administered alone. In the presence of 50mM of sodium caprate, however, the plasma level of this drug was markedly elevated, reaching a peak 10 min after administration. The effect of caprate on sodium ampicillin was similar to that on

Fig. 9 Enhanced Rectal Absorption of ABPC(60 mg/kg) by Absorption Promoters

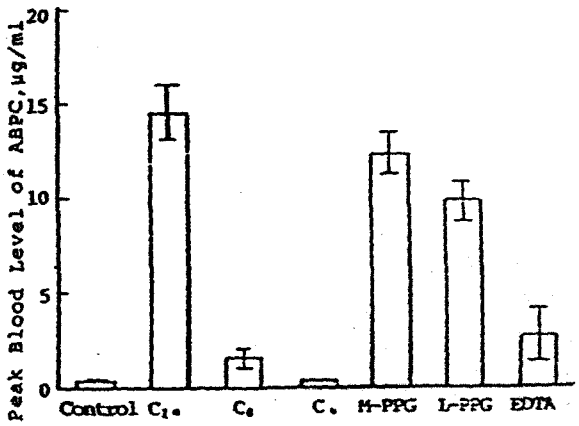
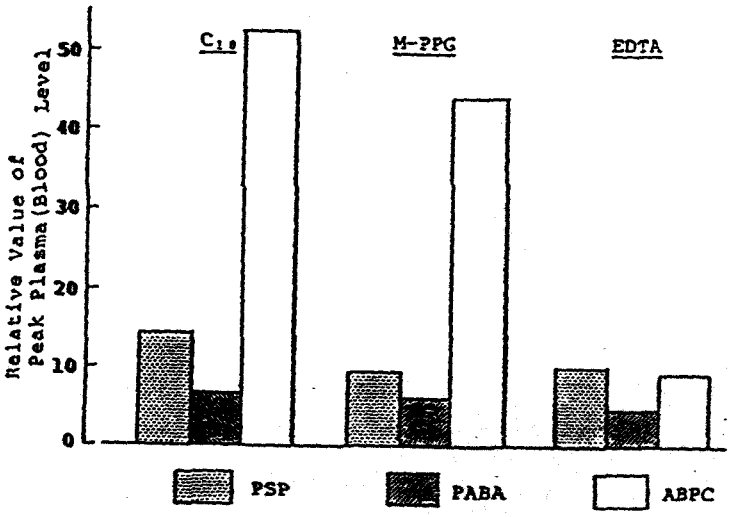


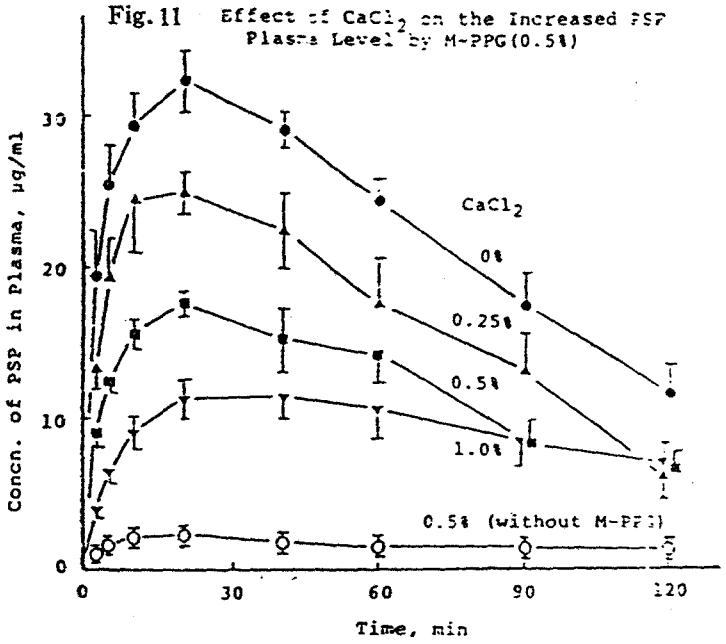
Fig. 10 Promoting Efficacy of Absorption Promoters for PSP, PABA and ABPC



PSP.

Also, in the presence of sodium caprate, the blood level of ampicillin was markedly elevated. The action intensity of absorption promoters, of course, depends on their concentrations. Fig. 14 and 15 represent the logarithmic values of the concentrations of absorption promoters in the solution administered into the rectal loop and the highest blood levels of target drugs achieved in the presence of absorption promoters in such concetrations.

It is indicated that C_{10} produces a stronger absorption promoting effect on sodium



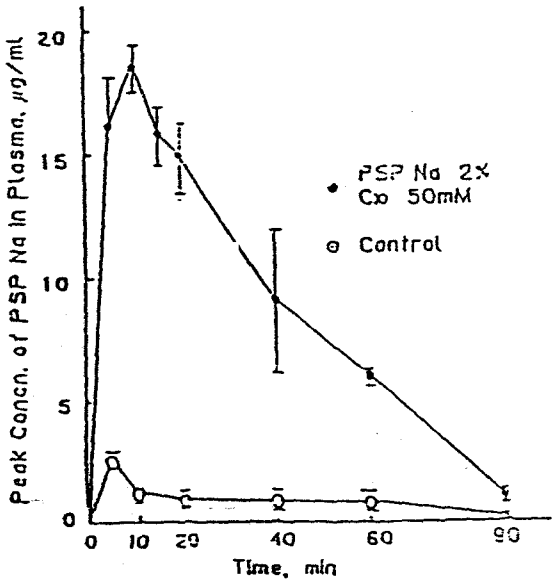


Fig. 12 Enhanced rectal absorption of PSP by sodium caprate in the rat

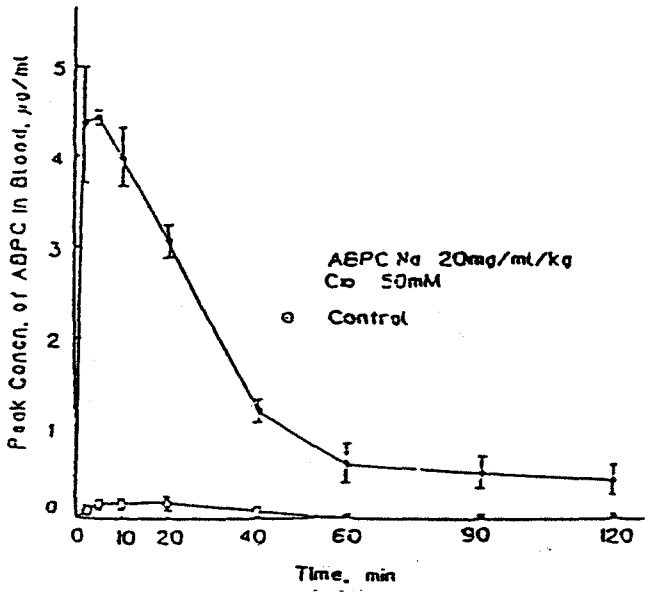


Fig. 13 Enhanced rectal absorption of sodium ampicillin by sodium caprate in the rat

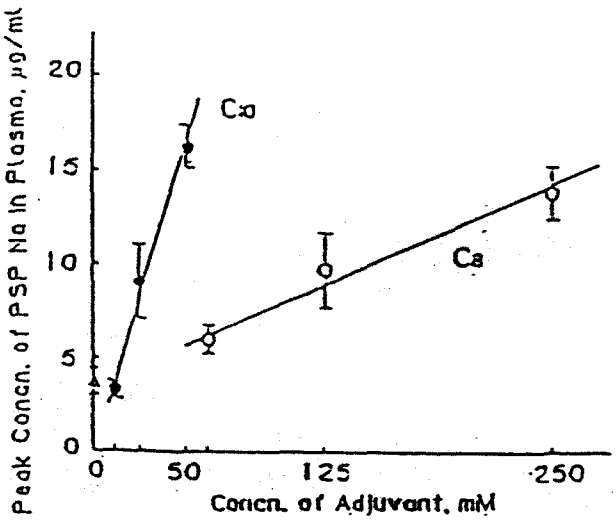


Fig. 14 Effect of adjuvant concentration on peak plasma level of PSP

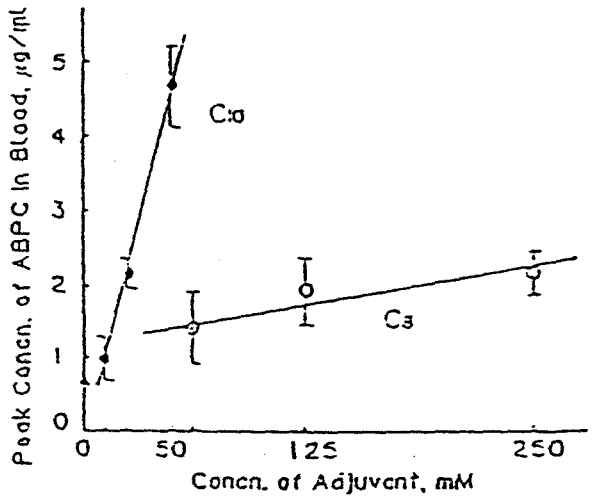


Fig. 15 Effect of adjuvant concentration on peak plasma level of ampicillin

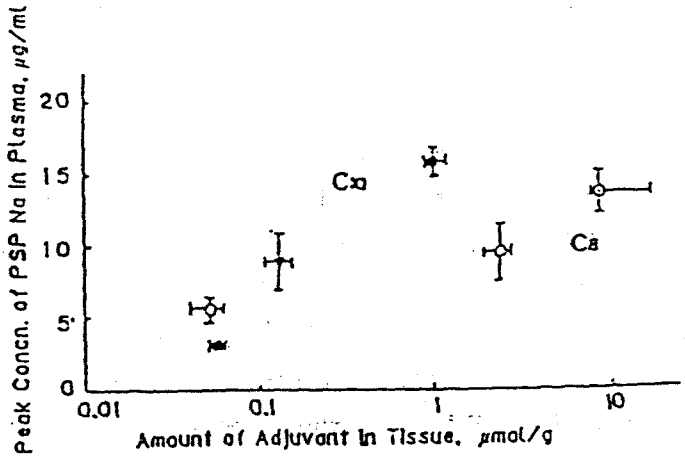


Fig. 16 Relations between peak plasma level of PSP and total amount of adjuvant accumulated in rectal tissue 10 min after administration

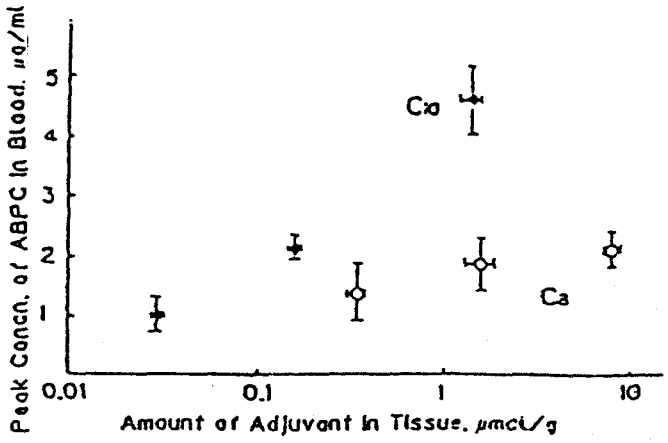


Fig. 17 Relations between peak plasma level of ampicillin and total amount of adjuvant accumulated in rectal tissue 10 min after administration

ampicillin as well as on PSP than C_8.

We considered that the differences in the effects of absorption promoters might be ascribable to differences in their affinities for the rectal tissue and Ca ion chelating activities.

As a measure of affinity for the rectal tissue, the rectal tissue levels of absorption promoters were determined when the blood level of each model drug reached a peak; i.e. 10min after administration. Fig. 16 shows the relationship between the number of moles of absorption promoters per g of the rectal tissue and the highest plasma level of PSP 10 min after administration.

When the results obtained with C_8 and C_{10} are assessed separately, it is found that the highest plasma level of PSP increases with increasing tissue level of each absorption promoter. However, the effects of C_8 and C_{10} can not be explained adequately by their tissue levels. Fig. 17 shows the results obtained with sodium ampicillin. The absorption promoting effect of C_{10} on sodium ampicillin can not be fully explained by the tissue level of this promoter either.

On the other hand, 1 mole of C_8 and C_{10} chelates 0.029 and 0.324 mole equivalent of Ca ion, respectively.

We assumed that the amount of Ca ion chelated by absorption promoters in the

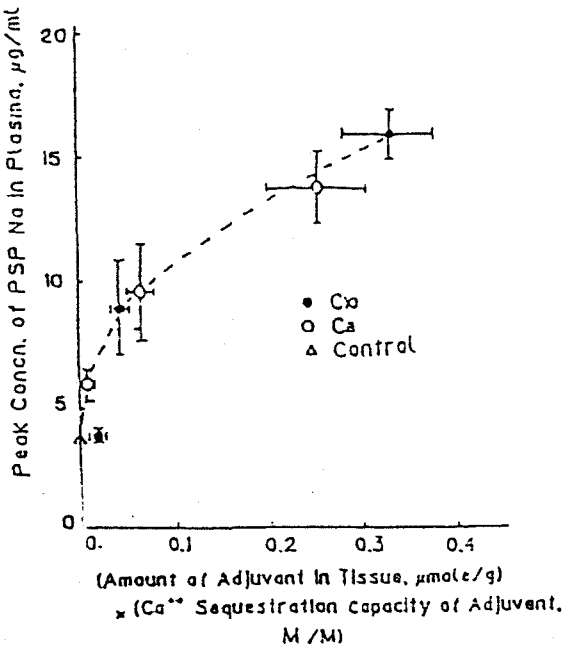


Fig. 18 Contribution of amount of Ca sequestration by adjuvant in rectal

tissue might be related to the intensity of their absorption promoting effects. Accordingly, the products obtained by multiplying the tissue levels of absorption promoters 10min after administration into the rectal loop at various concentrations by the Ca ion chelating activities were assessed for relationship with the highest blood levels of drugs.

As shown in Fig. 18, the Ca ion chelating activities of absorption promoters transported into the rectal tissue and the highest plasma levels of PSP. It is apparent that the absorption promoting effects of both C_8 and C_{10} can be adequately explained as a simple relationship.

Fig. 19 shows the results obtained with sodium ampicillin. The effects of both C_8 and C_{10} can also be adequately explained.

As described above, it is apparent that affinity for the rectal tissue and Ca ion chelating ability are related to the effects of absorption promoters.

Based on these experimental results, we propose the following mechanism as shown in Fig. 20. The intercellular space of the rectal epithelial layer is structurally tight owing

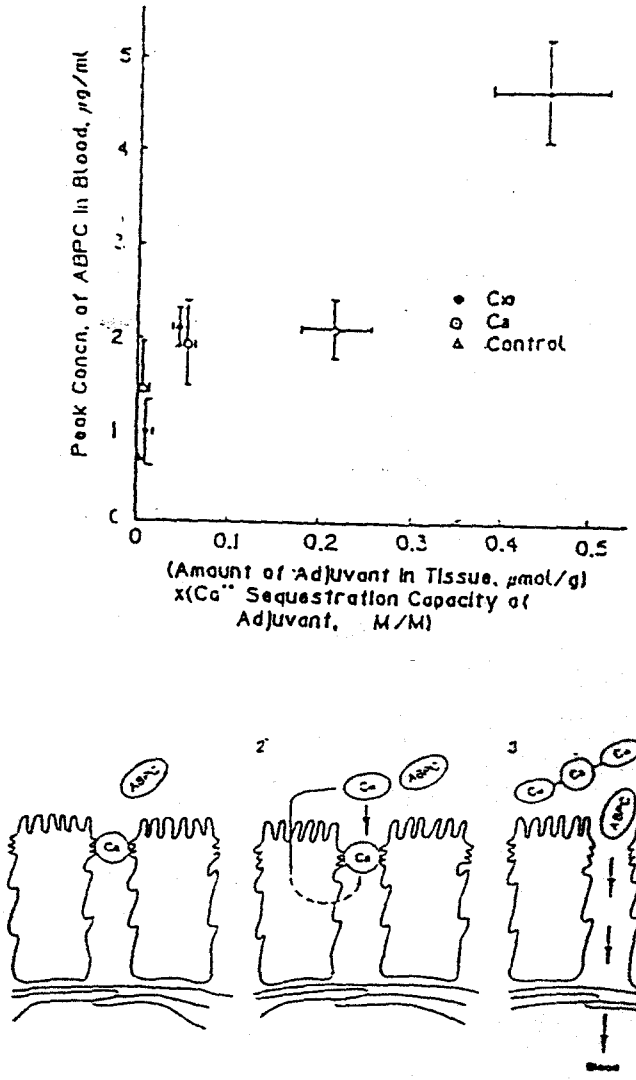


Fig. 20 A proposed mechanism of promoting effect on sodium caprate on the rectal absorption of ampicillin

to tight junction which may be composed of Ca and Mg ion-mediated peptide bonds. Ampicillin and PSP can not penetrate the epithelial layer because of this tight junction.

The absorption promoter C_8 or C_{10} is transported intracellularly or intercellularly into the intercellular space of the rectal epithelial layer and chelates Ca ion present in the tight junction.

As a result, the connective structure in the tight junction may be loosened to facilitate the penetration of drug molecules.

It is considered that the mechanism proposed in the present study is supported by the experimental results that the amount of Ca ion chelated by C_8 and C_{12} transported into the tissue was reflected in their absorption promoting effects.

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