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Possible factors behind the enhanced gastrointestinal absorption of griseofulvin from liquid organic acid ester solutions in rats

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Summary

Some possible factors involved in the enhanced gastrointestinal absorption of griseofulvin from ethyl acetoacetate, methyl propionate and methyl caproate solutions were investigated. The participation of lymphatic absorption to the enhanced griseofulvin was ruled out from findings that the ratio of lymphatic absorption to total systemic absorption was only 0.28%. The effect of esters on the intestinal membrane permeability was investigated employing in vitro rat everted intestine and in situ intestinal perfusion techniques. The transfer rate of griseofulvin from each vehicle across the everted intestine was increased in the following order: aqueous suspension $\leq$ ethyl acetoacetate < methyl caproate < methyl propionate. This order was coincident with the order of their absorption-enhancing potencies observed in vivo and a linear relationship was obtained between the transfer rate of griseofulvin from each vehicle in vitro and the value of the AUC or C_{max} obtained after intraduodenal administration. An increase in the exsorption rate of griseofulvin from blood vessel into small intestinal lumen was also observed in the presence of esters in the lumen aqueous perfusate. These results suggest that the enhanced intestinal absorption of griseofulvin from organic acid ester solution is mainly due to the increased membrane permeability caused by esters. The increased membrane permeability caused by methyl propionate and methyl caproate was also observed when phenolsulfonphthalein was used instead of griseofulvin.

Introduction

It is well known that the oral bioavailability of griseofulvin in man is increased with an increase of the amount of lipid in the diet (Crounse, 1961) and the improved oral bioavailability is also observed in rats when griseofulvin is administered together with corn oil (Kraml et al., 1962). Carrigan and Bates (1973) developed an emulsion dosage form as a potent delivery dosage form for griseofulvin based on the above facts.

As reported in a previous paper (Kadir et al., 1986), a marked increase in the gastrointestinal absorption of griseofulvin was also observed when the drug was administered orally as either a solution of ethyl acetoacetate, methyl propionate or methyl caproate in rats, whereas no enhanced absorption was observed when griseofulvin was administered as a solution of fatty acids such as

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acetic acid, butyric acid, caproic acid and capric acid. The enhancing potency of esters after intraduodenal administration was in the following order: aqueous suspension ≦ ethyl acetoacetate < methyl caproate < methyl propionate.

As possible mechanisms in the increase of the bioavailability when the drug was administered as a corn oil-in-water emulsion, Bates and Sequeira (1975) pointed out the importance of the inhibitory effect of lipid (emulsified corn oil) on the gastric emptying process of griseofulvin and the role of emulsified corn oil as a stimulator of bile secretion.

However, in the cases of ethyl acetoacetate, methyl propionate and methyl caproate, a marked enhancement in the absorption of griseofulvin was also observed even after intraduodenal administration in bile duct-ligated rats, although differences in the magnitude of enhanced absorption of griseofulvin were observed among the 3 esters. Therefore, it was considered that the contribution of the inhibitory effect of these vehicles on the gastric emptying process of griseofulvin and/or the contribution of bile could be ruled out from the main mechanism of the enhancing effect of ethyl acetoacetate, methyl propionate and methyl caproate.

In the present paper, other factors such as the effect of esters on the lymphatic absorption of griseofulvin and on the intestinal membrane permeability to the drug were investigated, since complete dissolution of griseofulvin in the dosing solution did not necessarily contribute to the enhanced intestinal absorption as seen in fatty acid solution.

Materials and Methods

Materials

Griseofulvin was purchased from Sigma Chemical Co. and used after passing through a 145-mesh screen (105 μm). Ethyl acetoacetate, methyl propionate, and methyl caproate of analytical grade were purchased from Wako Pure Chemical Ind., Ltd., and used as a vehicle without further purification. All other reagents were the finest grade available.

Determination of partition coefficient

The partition coefficient of griseofulvin was determined in a system with pH 7.4, phosphate buffer solution and a liquid organic ester. Griseofulvin was dissolved in ethyl acetoacetate, methyl propionate or methyl caproate at a concentration of 1 mg/ml. The organic ester layer containing griseofulvin was shaken with an equal volume of aqueous layer at 37°C for 5 h. After centrifuging at 2000 rpm for 5 min, aliquots were taken from both layers and analyzed for griseofulvin.

Animal studies

Adult male Wistar rats, 200–230 g, were used after fasting for 15 h prior to the experiments, but allowed free access to water.

Lymphatic absorption: rats were anesthetized by i.p. injection of pentobarbital and kept supine on a surface kept at 37°C. The thoracic lymphatic duct was exposed and cannulated by polyethylene tubing (PE 50, Clay Adams) filled with heparin solution. The tubing was fixed in this position by a drop of tissue cement (Aron Alpha A, Sankyo Co., Ltd.). Griseofulvin was introduced into the duodenum as solution of either ethyl acetoacetate or methyl caproate, or as an aqueous suspension at a dose of 20 mg/ml/kg in the same manner as described in the previous paper (Kadir et al., 1986). Lymphatic samples were collected via the cannulated tubing and blood samples were collected from the jugular vein at appropriate time intervals.

Permeation of griseofulvin across everted small intestines

Transfer of griseofulvin from ethyl acetoacetate, methyl propionate or methyl caproate across the everted rat intestine was investigated. The entire length of the small intestine was removed from rats fasted for 15 h and exsanguinated by decapitation. An initial 15-cm portion of the proximal small intestine was discarded and the following jejunum was used. The intestinal lumen was washed with cold saline to remove any solid materials. The intestine was everted and a 10-cm segment loop was made. As a serosal solution, 1 ml of pH 7.4 Ringer bicarbonate buffer was introduced into the inside of the loop. The loop was

placed into a test tube containing 10 ml of each ester solution of griseofulvin (5 mg/ml) prewarmed at 37 °C. After 15 min, the loop was removed and the serosal solution was analyzed for griseofulvin.

Exsorption of griseofulvin through small intestines. Rats were anesthetized by i.p. injection of pentobarbital and kept supine on a surface (37 °C) which maintained normal body temperature. The small intestines were exposed and cannulated both at pylorus and distal ends of the ileum with glass cannulae. After the ligation of the bile duct, the intestinal contents were washed out with a sufficient amount of pH 6.5 phosphate buffer (ionic strength = 0.15) prewarmed at 37 °C. Griseofulvin was administered to the tail vein at a dose of 20 mg/ml polyethylene glycol 300/kg. Immediately after the administration, phosphate buffer (pH 6.5) was perfused through the intestines for 45 min as a single perfusion. The perfusate was then changed to the same buffer containing 1% ethyl acetoacetate, 1% methyl propionate or 0.2% methyl caproate for 30 min, followed by perfusion with an initial buffer again for 45 min. The single perfusion was made at a flow rate of 3 ml/min. The perfusate was collected every 5 min, and the exsorption rates of griseofulvin were calculated from the amount of drug appearing in the perfusate.

Intestinal absorption of phenolsulfonphthalein from ester solution. An in situ intestinal loop experiment was performed. The small intestines of anesthetized rats were exposed by an abdominal incision and the bile duct was ligated. A polyethylene tubing (PE 50) was inserted in the distal direction at the duodenum and tied firmly to keep it in position. The distal end of the small intestine was tied to make a 10-cm intestinal loop. A drug solution was introduced into the loop through the polyethylene tubing. Phenolsulfonphthalein (PSP) was dissolved in dimethylsulfoxide (DMSO) at a concentration of 4%. The solution was diluted with either isotonic phosphate buffer (pH 6.5), ethyl acetoacetate, methyl propionate or methyl caproate to make a 0.2% solution of PSP. This solution was introduced into the intestinal loop at a dose of 4 mg PSP/2 ml/kg. The loop was removed 1 h after administration. The inside of the loop was washed out with a sufficient quantity of saline, and the washings were all combined together to make 100 ml by addition of saline. The amount of PSP absorbed was calculated from the unabsorbed amount observed in the washings.

Intestinal absorption of esters. An in situ absorption experiment was performed using a recirculating perfusion. Phosphate buffer (pH 6.5) solution of ethyl acetoacetate (15 mM), methyl propionate (15 mM) or methyl caproate (10 mM) and 0.2% fluorescein isothiocyanate-dextran (FITC-dextran, Sigma, FD-20) was recirculated through the entire small intestine for 1 h at a flow rate of 3 ml/min. FITC-dextran was used as a volume indicator. An aliquot of the perfusate was withdrawn periodically for analyses of esters and FITC-dextran.

Analytical methods

Griseofulvin in plasma, lymph or perfusate was determined by HPLC as described previously (Kadir et al., 1986). Ethyl acetoacetate, methyl propionate and methyl caproate in the perfusate were determined by HPLC. An aliquot (10 μl) of the perfusate was injected directly on the HPLC column. The HPLC was carried out with a HPLC UV 8 (Toyo Soda, Model II) apparatus equipped with a UV detector and a TSK-Gel (Toyo Soda, ODS-120T) reverse-phase column. Elution was done with 0.1 M acetic acid : acetonitrile (5 : 5, v/v) at ambient temperature and the flow rate was 1 ml/min. The eluted ethyl acetoacetate, methyl propionate, or methyl caproate was detected by measuring their UV absorption at 295 nm, 235 nm or 235 nm, respectively. The retention times of ethyl acetoacetate, methyl propionate and methyl caproate were 4.8 min, 5.9 min and 12.0 min, respectively.

FITC-dextran in the perfusate was determined as follows. Perfusate sample was appropriately diluted with pH 6.5 phosphate buffer solution and FITC-dextran was determined by fluorospectrophotometry (Hitachi, 204-A, Japan) at excitation and emission wavelengths of 490 nm and 516 nm, respectively.

Unabsorbed PSP in the intestinal loop was determined spectrophotometrically. The washings from the intestinal loop were centrifuged at 3000

rpm for 10 min. The supernatant was appropriately diluted with 1 N NaOH and PSP was determined spectrophotometrically (Shimadzu, UV 190) at 550 nm.

Results and Discussion

Partitioning of griseofulvin from organic layer to aqueous layer

As demonstrated in a previous report (Kadir et al., 1986), griseofulvin is highly dissolved in short-chain organic acids such as acetic acid (solubility = 4.45 g/100 ml) and pyruvic acid (43.7 g/100 ml). However, when griseofulvin was administered orally as a solution of such short-chain organic acids to rats, no enhancement in the bioavailability of griseofulvin was observed compared to that of aqueous suspension of griseofulvin. On the other hand, when administered as solution of either ethyl acetoacetate, methyl propionate or methyl caproate, a marked enhancement in the bioavailability was observed in the order of ethyl acetoacetate < methyl caproate < methyl propionate. Above findings implied that the increased gastrointestinal absorption of griseofulvin after administration as an ester solution was not only caused by the solution dosage form.

Prior to transfer of griseofulvin to the membrane from these liquid organic acid ester solutions in vivo, griseofulvin may be partitioned into the gastrointestinal fluid, since Grisafe and Hayton (1978a and b) reported that griseofulvin absorption from the micellar and oil phases was negligible compared to its absorption from the aqueous phase.

In the present study, as a preliminary experiment, the partition coefficient of griseofulvin was determined between vehicle and pH 7.4 phosphate buffer at 37°C. The partition coefficients were 372 in ethyl acetoacetate, 392 in methyl propionate, and 375 in methyl caproate. This result indicates that griseofulvin has a high affinity for all these vehicles and that there is no difference in the partition coefficients of griseofulvin among these vehicles. Therefore, partitioning of griseofulvin from organic acid esters to the aqueous layer does not seem to play an important role in the enhancement of griseofulvin absorption across intestinal membrane from the organic acid esters.

Lymphatic absorption of griseofulvin

It is well known that many lipophilic compounds such as cholesterol (Treadwell and Vahouny, 1968) and lipid-soluble vitamins (MacMahon et al., 1971; Yeung and Veen-Baigent, 1972) are mainly absorbed by the lymphatic route. Lymphatic absorption of griseofulvin was investigated from the viewpoint that if griseofulvin and the vehicle are absorbed simultaneously, griseofulvin may be preferentially absorbed via the lymphatic route. Noguchi et al., (1977a and b) reported that the lymphatic absorption of lipid-soluble compounds is influenced by oils in oil-in-water emulsions. To examine the possible contribution of lymphatic absorption of griseofulvin from the vehicles under study to the systemic bioavailability of griseofulvin, griseofulvin was administered intraduodenally to bile duct-ligated rats as a solution of ethyl acetoacetate or methyl propionate, or as an aqueous suspension, and the lymphatic and plasma levels of griseofulvin were determined. The lymphatic and plasma levels of griseofulvin are shown in Fig. 1 as a function of time. The time required to reach maximum lymphatic level was delayed 1 h compared to that of peak plasma levels in all cases, perhaps due to the slow lymphatic flow rate. The results are summarized in Table 1 in terms of bioavailability relative to i.v. administration (BA), peak plasma level (C_{max}, P), peak lymphatic level (C_{max}, L), ratio of peak concentration in lymph to that in plasma (L/P ratio), cumulative amount of griseofulvin obtained in lymph (CA), and the ratio of CA of griseofulvin obtained in lymph to the total amount absorbed into blood (CA ratio).

Noguchi et al. (1977b) reported that griseofulvin in a triolein-in-water emulsion is not absorbed exclusively through the lymphatic system because the L/P ratios were near unity after intraluminal administration of the emulsion or an aqueous suspension in rats with intact bile ducts (presence of bile juice). In the present study, the L/P ratio after administration of griseofulvin as an aqueous suspension was lower than unity, probably due to the absence of bile juice. On the other hand, the

TABLE 1

Lymphatic absorption of griseofulvin after intraduodenal administration in rats

	BA(%) [a] plasma	C_{max} (μg/ml)		L/P ratio [b]	CA (μg) [c] lymph	CA ratio [d] (%)
		P	L			
Aqueous suspension	31.55	0.35	0.17	0.49	0.94	0.08
	(1.22)	(0.02)	(0.02)	(0.04)	(0.19)	(0.05)
Ethyl acetoacetate	36.70	0.49	0.53	0.97	4.09	0.28
	(0.70)	(0.06)	(0.05)	(0.21)	(0.39)	(0.01)
Methyl propionate	79.94	1.17	0.78	0.61	3.20	0.10
	(1.60)	(0.06)	(0.09)	(0.02)	(0.38)	(0.01)

Each value represents the mean (S.D.), $n = 3$.

[a] AUC after intraduodenal administration/AUC after i.v. administration × 100%.

[b] Ratio of C_{max} in lymph : C_{max} in plasma.

[c] Cumulative amount of griseofulvin in lymph.

[d] Percent of cumulative amount in lymph to BA (CA/(dose of griseofulvin × BA (%)) × 100%). Dose of griseofulvin: 20 mg/kg.

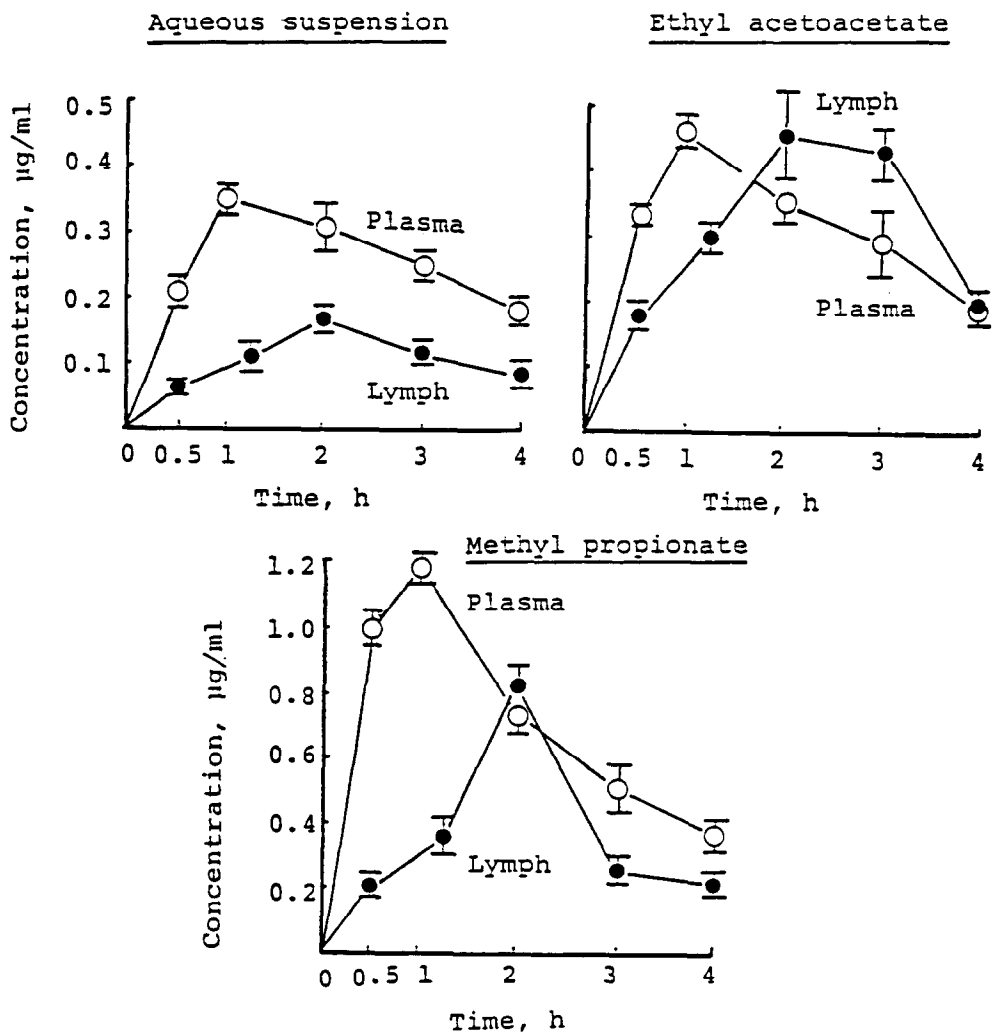

Fig. 1. Lymphatic absorption of griseofulvin from an aqueous suspension, ethyl acetoacetate solution and methyl propionate solution after intraduodenal administration at a dose of 20 mg/kg in rats. ○, plasma concentration; ●, lymphatic concentration. Each value represents the mean ± S.D. ($n = 3$).

L/P ratio after administration of griseofulvin in a solution of ethyl acetoacetate was significantly higher than after administration in aqueous suspension or methyl propionate solution, and the L/P ratio was almost unitary. These results imply that the lymphatic absorption of griseofulvin is slightly increased by administration of griseofulvin as an ethyl acetoacetate solution. However, small values of CA ratio as shown in Table 1 suggest that the contribution of the lymphatic absorption of griseofulvin to bioavailability is small or maybe nihil. Therfore, enhancement in griseofulvin absorption across small intestinal membranes should be caused by other factors such as modification in permeability of intestinal membranes. Effect of vehicles on transfer and exsorption of griseofulvin across small intestinal membrane were examined in vitro and in situ.

TABLE 2

Transfer rate of griseofulvin from mucosal to serosal fluid in everted rat small intestine, AUC_{0-10} and C_{max} of griseofulvin after intraduodenal administration in rats

Vehicle	Transfer rate of griseofulvin [c] (μg/min)	AUC [a] (μg·h/ml)	C_{max} [a] (μg/ml)
Aqueous suspension	0.207 ± 0.020	4.62 ± 2.39	1.08 ± 0.58
Ethyl acetoacetate	0.254 ± 0.015 [b]	5.66 ± 0.98	1.35 ± 0.38
Methyl propionate	0.480 ± 0.065 [b]	9.61 ± 0.54 [b]	3.26 ± 0.81 [b]
Methyl caproate	0.387 ± 0.015 [b]	7.31 ± 1.28 [b]	1.67 ± 0.52 [b]

Each value represents the mean ± S.D., $n = 3$–4.

[a] Obtained from a previous report (Kadir et al., 1986). Dose of griseofulvin: 50 mg/kg.

[b] Significantly different from aqueous suspension, $P < 0.05$.

[c] Initial concentration of griseofulvin in vehicles was 5 mg/ml.

Transfer of griseofulvin across the everted small intestines

As an another possible factor underlying the apparent enhancement in the absorption of griseofulvin following administration of solutions of ethyl acetoacetate, methyl propionate or methyl caproate, an increase in membrane permeability to griseofulvin by the vehicle was considered. The effect of vehicle on the intestinal membrane permeability to griseofulvin was examined using the everted rat small intestines. The results are shown in Table 2 in terms of transfer rate of griseofulvin from mucosal to serosal fluid. Significant increases in transfer rate of griseofulvin were observed in ethyl acetoacetate, methyl propionate and methyl caproate solutions compared to the case of an aqueous suspension, and the apparent transfer rate of griseofulvin increased in the following order: aqueous suspension < ethyl acetoacetate < methyl caproate < methyl propionate. Three possible causes will be considered to explain these findings. The first one is the increase in the concentration of griseofulvin available for the transfer by dissolving in esters compared to the aqueous suspension. The second cause may be that esters also permeate the serosal side and thereby increase the transfer of griseofulvin by increasing the affinity of griseofulvin to the serosal fluid. The third is the direct action of esters on the membrane to facilitate the transfer of griseofulvin. The first cause seems unlikely because much difference in the transfer rate of griseofulvin was observed among esters, whereas griseofulvin is dissolved in these esters. To examine the second possibility, similar experiments were carried out using buffer containing 5% bovine serum albumin (BSA) as a serosal solution, which increased the solubility of griseofulvin 5 times compared to that in buffer solution alone because of the high protein-binding characteristics of griseofulvin (80%) (solubility of griseofulvin: 11.6 μg/ml in buffer solution, and 58.0 μg/ml in buffer solution containing 5% BSA). However, no increase in the transfer rate of griseofulvin was observed. Thus, the second possible cause may also be ruled out. Therefore, the third cause seems most likely, i.e., esters will play a role on the membrane to facilitate to the transfer of griseofulvin. The order of transfer rate constant obtained in vitro was the same with the enhancing effect of ester on the intestinal absorption of griseofulvin in vivo. The increased C_{max} and AUC obtained after in situ intraduodenal administration of griseofulvin to bile duct-ligated rats as an ester solution (Table 2) were plotted against the transfer rate of griseofulvin obtained in this in vitro everted-intestine ex-

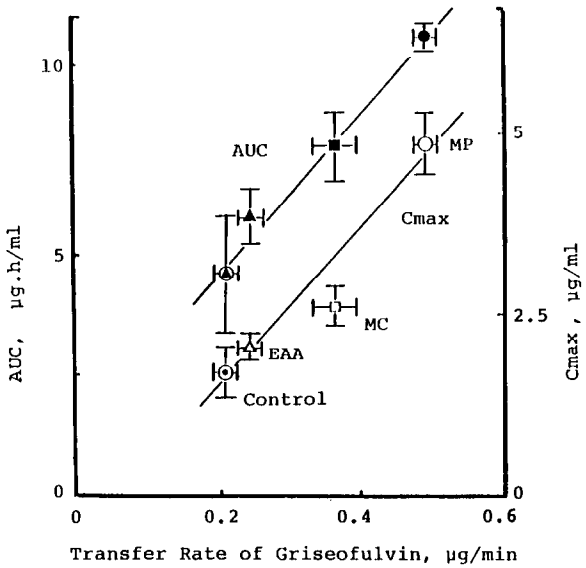

Fig. 2. Relationships between transfer rate of griseofulvin across rat everted intestine (in vitro) and AUC or C_{max} of griseofulvin obtained after intraduodenal administration at a dose of 50 mg/kg in rats (in situ). (▲, ○), aqueous suspension; (▲, △), ethyl acetoacetate; (●, ○), methyl propionate; (■, □), methyl caproate. Each value represents the mean ± S.E. ($n = 3$).

periment as shown in Fig. 2. The plots show a reasonable relationship between the transfer rate of griseofulvin in vitro and the value of AUC or C_{max} in situ. This relationship, especially among the 3 vehicles, may lead to a hypothesis that enhanced intestinal absorption of griseofulvin following intraduodenal administration depends on the magnitude of the increase in the intestinal membrane permeability to griseofulvin caused by esters.

Effect of esters on the exsorption of griseofulvin

The effect of esters on the intestinal membrane permeability to griseofulvin was also investigated by evaluating the effect on the exsorption rate of griseofulvin into rat small intestine using an in situ single perfusion technique. The results are shown in Fig. 3. When pH 6.5 phosphate buffer was perfused through small intestines, the time course of the rate of exsorption of griseofulvin was parallel to the time course of plasma level as shown in Fig. 3a after 20 min. When the perfusate was changed from buffer solution to 1% ethyl acetoacetate, 1% methyl propionate or 0.2% methyl caproate, the exsorption rate of griseofulvin was clearly increased. The enhanced exsorption rate then returned to its original value when the perfusate was switched again to the initial buffer solution. The increase in the exsorption of griseofulvin may be explained from the following two mechanisms. One is the high affinity of griseofulvin for esters in the perfusate and another is the modification of membrane permeability to griseofulvin by esters. However, from the results that little difference was observed in the solubility of griseofulvin among the perfusates (solubility of griseofulvin = 11.6 μg/ml in buffer solution, 13.8 μg/ml in 1% ethyl acetoacetate–buffer solution, 13.3 μg/ml in 1% methyl propionate–buffer solution, and 12.6 μg/ml in 0.2% methyl caproate–buffer solution), the former mechanism was ruled out. The small role of high affinity of griseofulvin for the perfusate to the increased exsorption will be recognized also from the results using BSA in the everted intestine study. Accordingly, the increase of exsorption of griseofulvin by esters will be explained from the possible modification of the membrane permeability to griseofulvin. The results also suggest that this modification in the permeability of small intestinal membranes occurs reversibly when the ester solution of griseofulvin is introduced into the small intestines.

The absorption of esters by rat small intestine was examined using an in situ recirculating technique. The time course of absorption and remaining percent of ethyl acetoacetate, methyl propionate and methyl caproate in the perfusing solution are shown in Fig. 4.

The disappearance of each ester from the perfusate was fast and followed apparent first-order kinetics with half-lives of 15–20 min. No significant difference in the disappearance rate constant was observed among the three vehicles. These findings also suggest that griseofulvin might not be transfered together with the vehicle. Thus, each ester penetrated in the membrane may be considered to modify the membrane permeability.

Inui et al. (1974) reported that the absorption of drugs in the presence of short-chain fatty acids may be mainly affected by physiological factors such as the absorption of water and the alteration

of microclimate pH on the absorptive membrane. Grisafe and Hayton (1978a and b) reported that the absorption rate of griseofulvin was decreased in the presence of premicellar concentration of short- and medium-chain fatty acids in the perfusate recirculated through a segment of in situ rat jejunum, although the fatty acids increased the absorption rate of water from the perfusate. In a previous study (Kadir et al., 1986), we showed that the absorption of griseofulvin was not increased after oral administration of short-chain fatty acid solution, whereas the absorption of griseofulvin was markedly increased by their esters. Methyl butyrate is recognized to exist as an ester on the mucosal surface and is hydrolyzed to butyric acid within the epithelial cells (Inui et al., 1974). Each ester used in the present study may be hydrolyzed within the epithelial cell. Thus, only esters may increase the membrane permeability to griseofulvin by acting on the mucosal surface.

Effect of esters on the intestinal absorption of PSP

To further examine the effects of esters on the intestinal membrane permeability, PSP was used. PSP, a highly water-soluble compound, is known to be poorly absorbed from the small intestine because of its low lipophilicity. In the case of PSP, a possible contribution of the increase in the solubility of drugs in esters to absorption will be ruled out because PSP is sufficiently soluble in aqueous solution. Absorption of PSP from isotonic aqueous solution or various esters containing 5% DMSO is shown in Fig. 5. DMSO was used to solubilize PSP in esters. The intestinal absorption percent of PSP was 8.40 ± 0.53% after administration of PSP buffer solution containing 5% DMSO.

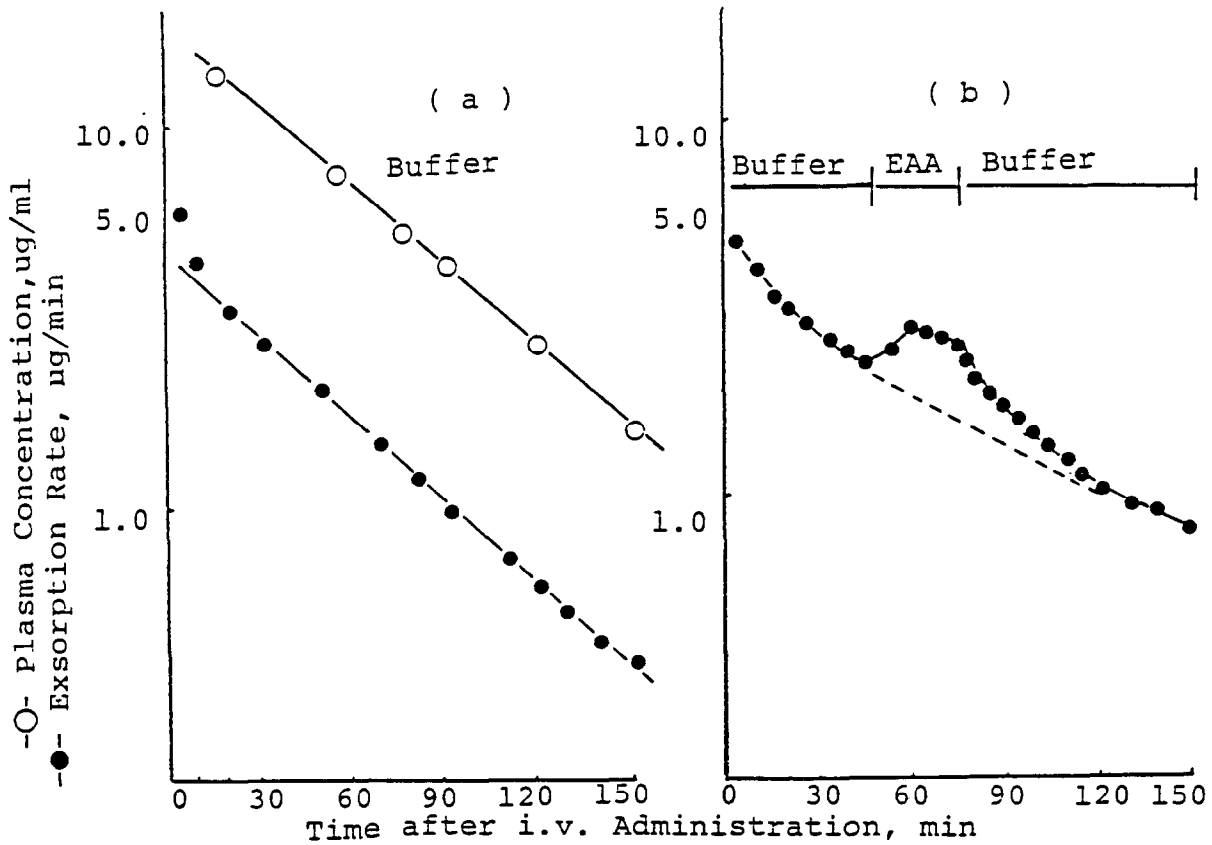

Fig. 3. Effect of buffer solution alone (a), 1% ethyl acetoacetate (b), 0.2% methyl caproate (c), or 1% methyl propionate (d) on the exsorption of griseofulvin to rat small intestine at pH 6.5 following i.v. administration at a dose of 20 mg/kg. The plasma concentration of griseofulvin is also shown in (a).

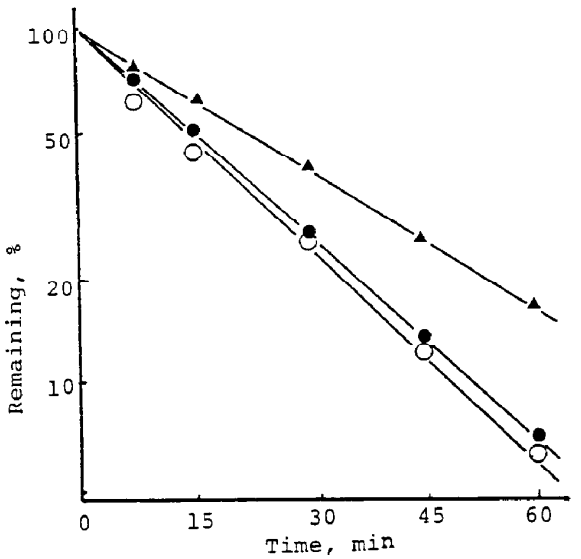

Fig. 4. Time course of the intestinal absorption of ethyl acetoacetate, methyl propionate and methyl caproate at pH 6.5 in rats. Initial concentration in perfusate: 15 mM ethyl acetoacetate (▲); 15 mM methyl propionate (●); 10 mM methyl caproate (○). Each plot represents the mean for 3 rats.

A marked promoting action for the intestinal absorption of PSP was observed with methyl propionate or methyl caproate solution. Methyl propionate showed a greater effect. Thus modifying actions of methyl propionate and methyl caproate for the membrane permeability to PSP were also observed. These findings suggest that the enhanced intestinal absorption of griseofulvin administered as an ester solution is not due to the dissolution of griseofulvin in the dosing solution, but to the increase in the membrane permeability caused by esters.

Further investigations into, e.g., the relations between the promoting action of esters and the characteristics of the drugs administered, effects of esters on the binding of drug to brush-border membrane, and the effect of esters on the membrane fluidity, will be necessary to clarify the mechanism of action of the esters at the cellular level and confirm the enhanced absorption hypothesis.

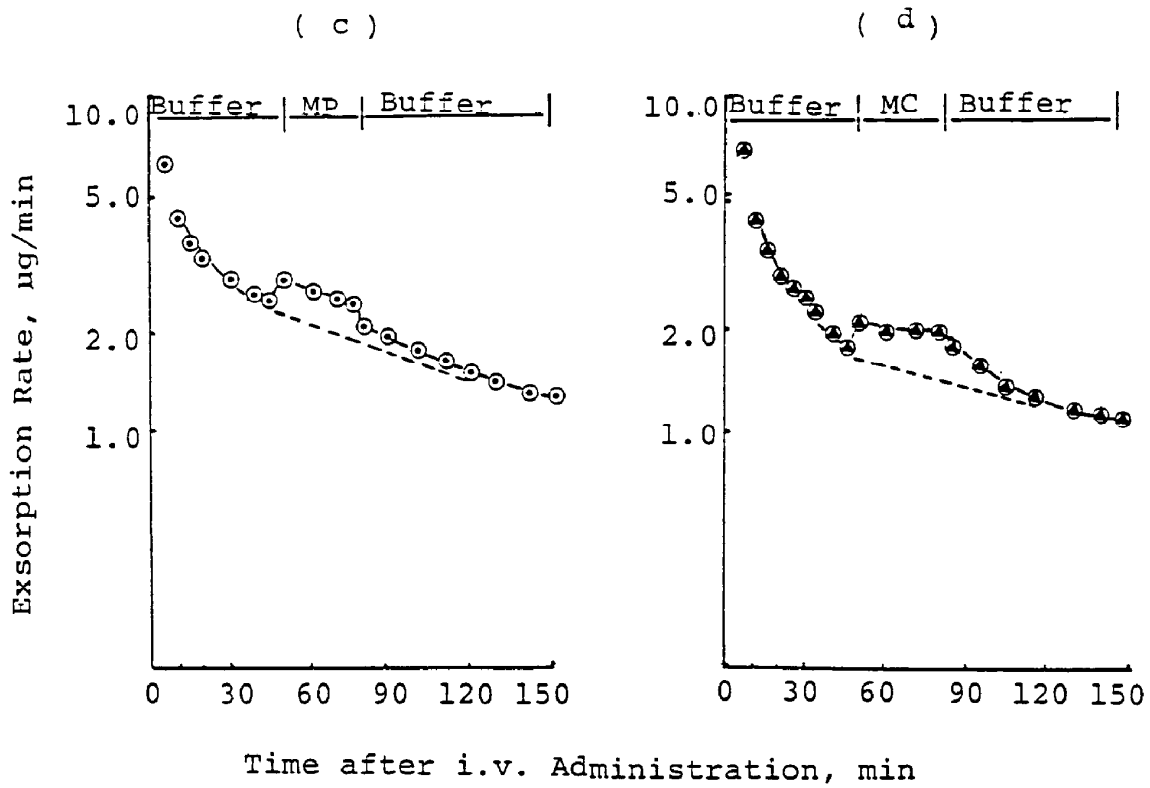

Fig. 3 (contd.).

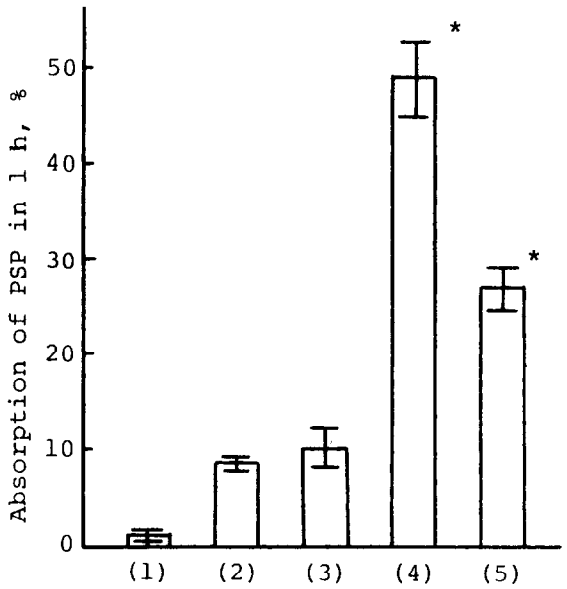

Fig. 5. Intestinal absorption of PSP from aqueous, ethyl acetoacetate, methyl propionate and methyl caproate solutions for 1 h. Dose: 4 mg PSP/2 ml/kg. (1) pH 6.5 phosphate buffer; (2) buffer +5% DMSO; (3) 95% ethyl acetoacetate +5% DMSO; (4) 95% methyl propionate +5% DMSO; (5) 95% methyl caproate +5% DMSO. Each value represents the mean ±S.E.M. ($n = 3$–4). *, $P < 0.01$, compared with buffer+5% DMSO

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