Effects of Short and Medium Chain Fatty Acids on Absorption of Lipophilic Drugs from Perfused Rat Intestine

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Abstract □ The absorption rates of griseofulvin and prednisolone were measured from solutions that were recirculated through a segment of *in situ* rat jejunum. When premicellar concentrations of butyric, octanoic, or dodecanoic acid were present in the perfusate, the griseofulvin absorption rate decreased while that of prednisolone increased. The fatty acids also increased the absorption rate of water from the perfusate, and the effect of butyric acid was attributed primarily to this increase. The absorption-altering effects of octanoic and dodecanoic acids could not be attributed solely to their effects on water absorption nor to their effects on the surface tension of the perfusate. The effects of octanoic and dodecanoic acids were explained by postulating different rate-limiting barriers to the absorption of prednisolone and griseofulvin.

Keyphrases □ Fatty acids, various—effects on absorption of lipophilic drugs from perfused rat intestine □ Absorption—lipophilic drugs from perfused rat intestine, effects of various fatty acids □ Lipophilic drugs—prednisolone and griseofulvin, effects of fatty acids on absorption from perfused rat intestine □ Griseofulvin—absorption from perfused rat intestine, effects of fatty acids □ Prednisolone—absorption from perfused rat intestine, effects of fatty acids

The presence of a mixed micellar phase composed of sodium taurodeoxycholate, oleic acid, and monoolein in perfusates recirculated through the *in situ* rat intestine reduced the absorption rate of griseofulvin (1). The absorption rate was further reduced when emulsified triolein was included in the perfusate. The reduced absorption rate of griseofulvin was attributed primarily to partitioning of the drug into the micellar and triolein phases from which it was not appreciably absorbed. The griseofulvin absorption rate from the micellar phase was reduced more than could be explained by micellar complexation of the drug. A possible explanation for the additional decrease was that a component of the micellar phase reduced the permeability of the intestinal epithelium. This study, therefore, explored the effects of fatty acids on the permeability of the *in situ* intestinal mucosa.

BACKGROUND

Fatty acids may alter the permeability of the intestinal mucosa to drugs. For example, butyric acid inhibited the absorption of the anionic drugs sulfisoxazole and salicylic acid; it enhanced the absorption of the neutral drugs caffeine and sulfanilamide and of the cationic drugs metoclopramide and quinine (2). Low molecular weight alcohols also appear to alter drug absorption. Hexanol reduced the absorption rate of sulfapyridine and salicylic acid and increased the absorption rate of prednisolone (3). Conversely, the absorption rate of theophylline from the rat intestine was increased by glycerol (4), propylene glycol (4), and ethanol (5).

The intestinal absorption of drugs from perfusates that contained solubilized long chain fatty acids also was investigated. The bile salt sodium taurocholate, alone or together with a low concentration of oleic acid, increased procainamide absorption in the rat; when a high concentration of oleic acid was used, procainamide absorption decreased (6). Furthermore, the absorption of 2-allyloxy-4-chloro-*N*-(2-diethylaminoethyl)benzamide hydrochloride, a drug with a higher chloroform–pH 6.5 phosphate buffer partition coefficient than procainamide, was unchanged by sodium taurocholate and oleic acid (6). These effects were attributed to modification of the permeability of the intestinal membrane and micellar complexation of the drug. However, another study (7) reported that oleic acid, slightly in excess of its solubility, had no detectable effect on the absorption of salicylic acid, salicylamide, and 4-aminoantipyrine.

These results suggest that fatty acids may alter the permeability of the intestinal mucosa to drugs. The direction of the change in permeability appears to depend in part on the properties of the drug. While representative water-soluble drugs have been studied, the effects of fatty acids on the permeability of the intestine to lipophilic drugs have not been well characterized. In this study, the effects of fatty acids on the absorption rates of griseofulvin and prednisolone were examined; both drugs are lipophilic and poorly soluble in water. The fatty acids used were butyric, octanoic, and dodecanoic because they are sufficiently water soluble to be incorporated in perfusate solutions without the aid of bile salts at pH values compatible with the intestine. They also differ in lipophilicity.

EXPERIMENTAL

Materials—Sodium butyrate[1], octanoic acid[2], dodecanoic acid[1], griseofulvin[3], prednisolone[3], and tromethamine[4] were used as received. ^{3}H-Prednisolone[5] was dissolved in alcohol and stored at 5°. The radiochemical purity (>88%) of ^{3}H-prednisolone was determined by TLC on glass plates coated with silica gel G and developed with benzene–2-propanol (4:1). All other reagents and solvents were reagent grade.

Intestinal Clearance—Male Sprague-Dawley rats, 180–360 g, were housed in wire mesh cages in a room maintained at approximately 20° and lighted automatically 12 hr/day. The clearance of prednisolone and griseofulvin from solutions recirculated at 6.5 ml/min through a 20-cm segment of *in situ* jejunum was measured as described previously (1). When fatty acid was present in the perfusate, its concentration was maintained relatively constant by infusing an aqueous solution of the fatty acid into the perfusate. The infusion rate was sufficient to compensate for loss of fatty acid due to absorption by the intestine and removal of samples (Fig. 1). To assure complete solubilization of the fatty acid, the pH of the infused solution was 6.2 for butyrate and octanoate and 8.4 for dodecanoate.

The intestinal solution initially contained either 280 μM prednisolone (0.1 μCi of ^{3}H-prednisolone/ml) or 23 μM griseofulvin. When butyrate or octanoate was studied, the buffer was 68 mM sodium phosphate and was made isotonic with 87 mM sodium chloride. The sodium chloride concentration was not reduced when fatty acid was present. Perfusates that contained dodecanoate were at pH 8.4 in isosmotic tromethamine buffer (250 mM).

The intestinal perfusate was sampled periodically, and the drug concentration was determined. The drugs were absorbed by apparent first-order kinetics (Fig. 2). Semilogarithmic plots of the fraction of initial drug concentration *versus* time gave straight lines when fitted by the least-squares method. The initial point was omitted from the fit to ensure stationary-state conditions. The absorption rate constants were determined from the slopes of the fitted lines.

The absorption rate constants were converted to clearance per centimeter of intestine as described previously (1). The water absorption rate was calculated as $(V_1 + V_2 - V_3)/(XD)$, where V_1 is the volume of buffer added to the drug solution to maintain a constant volume, V_2 is the volume of fatty acid solution infused, V_3 is the total volume of samples, X

[1] Matheson, Coleman and Bell, Norwood, Ohio.
[2] Nu Chek Prep, Elysian, Minn.
[3] Sigma Chemical Co., St. Louis, Mo.
[4] Pfaltz & Bauer, Stamford, Conn.
[5] Amersham/Searle Corp., Des Plaines, Ill.

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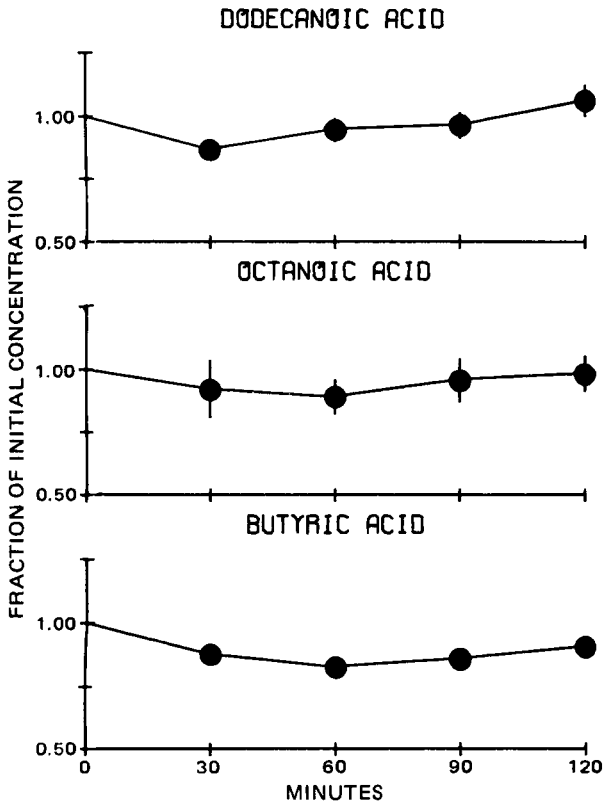

Figure 1—*Fractions of the initial concentration of dodecanoic acid (4 mM), octanoic acid (6 mM), and butyric acid (60 mM) remaining in the intestinal solution as a function of time. Each point represents the mean from six experiments, and bars indicate ±1* SE.

is the length of the intestinal segment, and D is the duration of the experiment. The fatty acid infusion rates were determined experimentally prior to measurement of the drug absorption rate constants (Table I).

Surface Tension—The surface tension of the perfusates was determined by the du Nouy ring detachment method[6]. The surface tension was plotted against the logarithm of the fatty acid concentration, and the critical micelle concentration (CMC) was estimated. Fatty acid concentrations used in the intestinal perfusates were below the CMC.

Analytical Methods—Octanoic and dodecanoic acids were separated and analyzed spectrophotometrically as described previously (1, 8). Butyric acid in 0.3-ml samples of intestinal perfusate was determined by GLC. Samples were mixed with 0.1 ml of aqueous 1-propanol, which was used as an internal standard; approximately 1 μl was injected onto a stainless steel column, 0.31 cm (0.125 in.) o.d. × 1.8 m (6 ft), packed with 80–100-mesh Porapak Q. The temperatures of the injection port, oven, and flame-ionization detector were 250, 230, and 250°, respectively. The flow rates of helium, hydrogen, and air were 55, 65, and 300 ml/min, respectively.

A plot of the ratio of the peak height of butyric acid to that of propanol *versus* butyric acid concentration was linear over the 10–70-m*M* range. Analysis of blank samples of intestinal perfusate did not produce peaks that would interfere with the propanol or butyric acid peaks.

Tritium was determined in intestinal perfusate by mixing 50–200-μl samples with 10 ml of scintillation fluid[7] and counting in a liquid scintillation spectrometer[8]. The counting efficiency of the system was 30–40%; quench corrections were made by the channels-ratio method.

RESULTS AND DISCUSSION

The fatty acids significantly altered the absorption rates of griseofulvin and prednisolone. The disappearance rate of griseofulvin from the intestinal perfusate was decreased significantly by octanoic and dodecanoic acids, but butyric acid produced no detectable effect (Table II). The disappearance rate of prednisolone was increased significantly by the three fatty acids (Table II).

Table I—Infusion Rates that Maintain a Constant Concentration of Fatty Acid in the Intestinal Perfusate

Fatty Acid	Infusion Rate[a], mg/ml	Intestinal Clearance[b], μl/min/cm
Butyric, 60 m*M*	0.92	8.19
Octanoic, 6 m*M*	0.36	20.10
Dodecanoic, 4 m*M*	0.13	7.52

[a] Includes replacement of losses due to sampling. Samples of 0.3 ml were removed at 30-min intervals. [b] Calculated by infusion = clearance × concentration in the perfusate. Corrected for the rate of removal of samples.

One mechanism that accounts for part of the absorption-altering property of the fatty acids involves their effect on the water absorption rate by the intestine. The drug absorption rate is related directly to the water absorption rate through a solvent drag mechanism (4, 5). The absorption rates of both griseofulvin and prednisolone were proportional to the water absorption rates observed (Figs. 3 and 4); griseofulvin was more sensitive than prednisolone to the water flux. All three fatty acids increased the absorption rate of water (Table III), even though they also increased the osmotic pressure of the intestinal perfusate. Thus, the increased absorption rate of prednisolone induced by butyric acid is primarily a secondary effect that results from an increase in the water absorption rate.

When differences in water absorption rates are taken into account, the absorption-altering effects of the fatty acids apparent in Table II are increased for griseofulvin and decreased for prednisolone. However, the absorption-altering effects of octanoic and dodecanoic acids cannot be explained solely by their ability to increase the water absorption rate (Fig. 5). The effects of these fatty acids on absorption appear to involve additional mechanisms.

No significant relationship was observed between the effects of the fatty acids on absorption and their effects on the surface tension of the perfusates (Table II). For example, 4 m*M* dodecanoic acid caused a larger decrease in surface tension than did 24 m*M* octanoic acid, but it had a smaller effect on the absorption rate of the two drugs.

While the fatty acids changed the absorption rates of griseofulvin and prednisolone in opposite directions, the magnitudes of the changes were similar (Table II), especially when the effects of altered water flux were

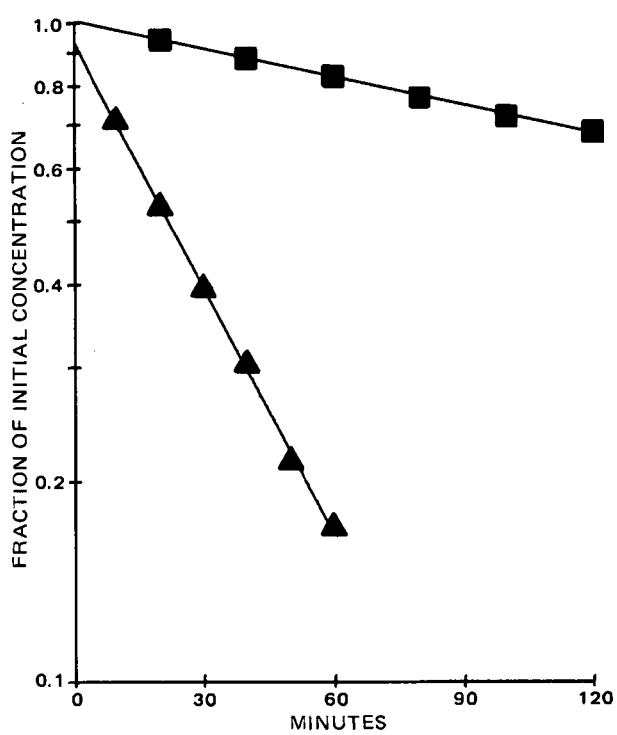

Figure 2—*Disappearance of prednisolone (■) and griseofulvin (▲) from the intestinal perfusate. Initial concentrations were 280 and 23 μM, respectively. Each point is the mean from six experiments.*

[6] Cenco-DuNouy interfacial tensiometer model 70545, Central Scientific Co., Chicago, Ill.
[7] Aquasol, New England Nuclear, Boston, Mass.
[8] Packard Tri-Carb model 3320, Packard Instrument Co., Downers Grove, Ill.

Table II--Effects of Fatty Acids on Perfusate Surface Tension and Intestinal Clearance of Griseofulvin and Prednisolone

Perfusate	Surface Tension Reduction, dynes/cm	Intestinal Clearance, μl/min/cm[a]		Change in Clearance, % of Control			
		Griseofulvin	Prednisolone	Griseofulvin	Prednisolone	Griseofulvin[b]	Prednisolone[b]
pH 6.2 Phosphate buffer							
Control		9.44 (1.19)	1.49 (0.40)	—	—	—	—
Butyric acid, 60 m*M*	0.0	9.50 (0.58)	2.30 (0.40)	1.0	54.4	−27	11
Octanoic acid, 6 m*M*	17.8	8.91 (1.41)	—[c]	−5.6	—[c]	−13	—[c]
Octanoic acid, 12 m*M*	24.7	7.59 (2.59)	—[c]	−19.6	—[c]	−34	—[c]
Octanoic acid, 24 m*M*	31.5	5.47 (0.78)	2.75 (0.28)	−42.1	84.6	−58	58
pH 8.4 Tromethamine buffer							
Control		6.32 (1.13)	1.07 (0.15)	—	—	—	—
Dodecanoic acid, 4 m*M*	48.1	4.20 (0.65)	1.69 (0.31)	−33.5	57.9	−45	31

[a] Mean from six experiments; standard deviation in parentheses. [b] Clearance values adjusted to zero water flux; see Figs. 3 and 4. [c] Not determined.

removed. This similarity suggests that the fatty acids act by changing one aspect of the absorption process and that this change causes the apparent permeability of the intestine to the drugs to change in opposite directions. Thus, griseofulvin and prednisolone possibly are absorbed by two different routes. The change induced by the fatty acids in the intestine augments the route for prednisolone while simultaneously depressing the route for griseofulvin. Although such a mechanism may exist, it is difficult to envisage a specific change in the structure or function of the intestinal epithelium that would plausibly explain the observed effects of the fatty acids.

An alternative explanation for the effects induced by the fatty acids is that the permeability of the mucosa to griseofulvin and prednisolone is controlled by two separate barriers. The permeability of the barrier for prednisolone would then be increased by the fatty acids while the permeability of the barrier for griseofulvin would be decreased. For example, intestinal blood flow or an aqueous unstirred layer could limit the absorption rate of griseofulvin while the permeability of the intestinal epithelium could limit the absorption rate of prednisolone.

The average blood flow rate to the proximal 40% of the small intestine of 258 ± 7-g male Sprague-Dawley rats, anesthetized with 1.3-mg/g doses of urethan, was 1.10 ml/min/g of wet weight (9). The weight of the 20-cm segment perfused in the present study was approximately 1 g; the blood flow rate to the perfused intestine is, therefore, approximately 55 μl/min/cm. However, studies of the blood-to-lumen flux of barbital in the perfused rat ileum revealed that subepithelial capillary blood flow available for transport of absorbed substances amounted to 50.3% of the total blood flow to the intestine (10). Thus, the effective intestinal blood flow to the perfused segment is approximately 28 μl/min/cm. This value is probably an overestimate since equilibration of absorbed drug between erythrocytes and plasma may not be complete during the short time that blood resides in the epithelial capillary. Also, there is the possibility of a countercurrent exchange in the villus that removes drug from the blood exiting the villus (11). The control intestinal clearance of griseofulvin averaged 9.44 μl/min/cm of intestine, and it is possible that griseofulvin clearance was determined primarily by the intestinal blood flow rate. If the fatty acids reduced the blood flow rate through subepithelial capillaries, griseofulvin clearance also would be reduced.

Another potentially important barrier to the intestinal absorption of rapidly absorbed compounds is an unstirred water layer adjacent to the mucosal surface (*e.g.*, 12–14). Estimates of the thickness of this layer are 50–300 μm, depending on the agitation intensity. Water flux across the membrane can affect the thickness of this barrier significantly (15), as can the movement of microvilli (16). A clearance constant for the unstirred layer can be estimated as $D(A/h)$, where D, the diffusion coefficient in water, is 1×10^{-5} cm²/sec; h, the thickness of the unstirred layer, is 50 μm; and A is the surface area of a right cylinder of 0.4-cm diameter. The estimated clearance, 15 μl/min/cm of intestine, is in the range observed for griseofulvin, although the uncertainty in A and h could cause a large error. The fatty acids may have decreased griseofulvin clearance by increasing h, perhaps by stimulating the mucus secretion.

Since the intestinal clearance of prednisolone is considerably less than that of griseofulvin, the primary barrier to prednisolone absorption is probably not blood flow or a stagnant aqueous layer. Thus, a change in these parameters should not have a discernible effect on its absorption. Recent work using the same technique as was used here demonstrated that the permeability of the intestinal epithelium to prednisolone was increased by a number of substances in addition to fatty acids (Table IV). The capacity of the various additives to increase the absorption rate of prednisolone appears to be related directly to the lipophilicity of the additive. Earlier studies with substituted amides and, in particular, di-

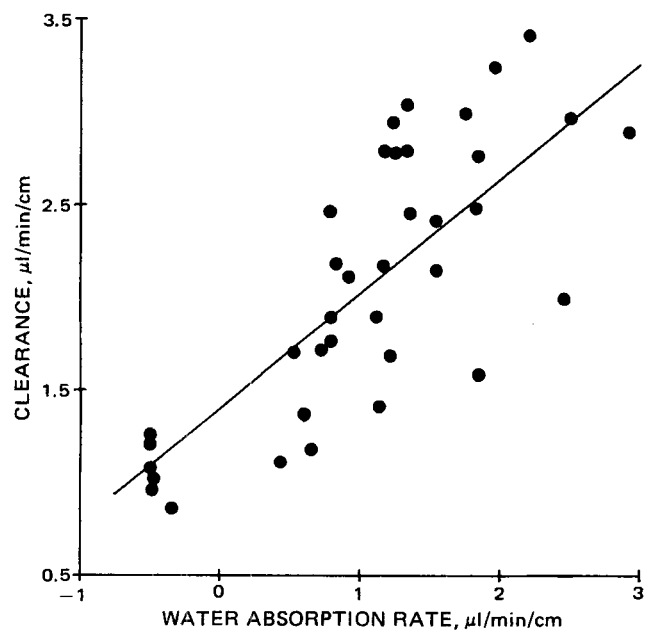

Figure 3—*Clearance of prednisolone* versus *water absorption rate. Each point represents a single experiment. The equation of the line, fit by the least-squares method, is* y = *0.618*x + *1.40.*

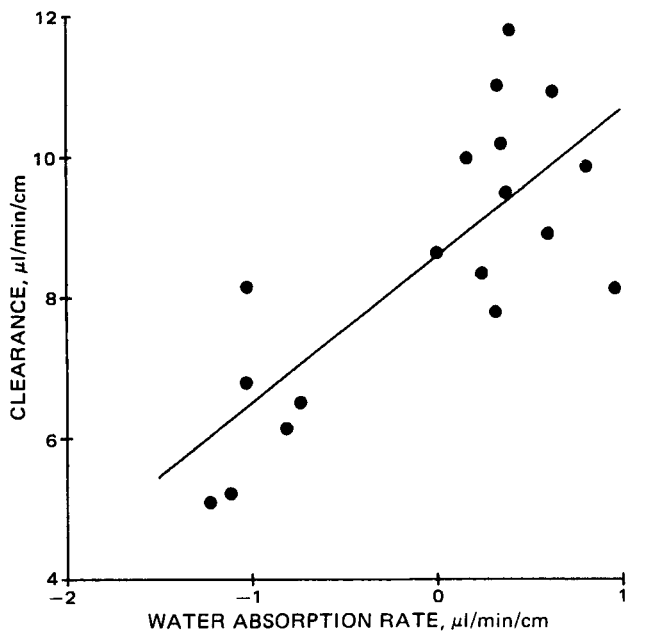

Figure 4—*Clearance of griseofulvin* versus *water absorption rate. Each point represents a single experiment. The equation of the line, fit by the least-squares method, is* y = *2.08*x + *8.58.*

Table III—Effect of Fatty Acids on the Absorption Rate of Water from the Perfused Rat Intestine

	Absorption Rate[a], μl/min/cm of Intestine				
	Control[b]	Control[c]	Butyric Acid[d]	Octanoic Acid[e]	Dodecanoic Acid[f]
Prednisolone	0.70 (0.25)	−0.47 (0.06)	1.20 (0.30)[g]	0.87 (0.19)	−0.23 (0.08)[g]
Griseofulvin	0.41 (0.20)	−0.99 (0.19)	1.55 (0.25)[g]	0.91 (0.35)[g]	−0.25 (0.23)[g]
Mean	0.55 (0.27)	−0.73 (0.31)	1.38 (0.32)[g]	0.89 (0.27)[g]	−0.24 (0.16)[g]

[a] Mean from six experiments with the standard deviation in parentheses. [b] With 68 m*M* sodium phosphate and 87 m*M* sodium chloride, pH 6.2. [c] With 250 m*M* tromethamine, pH 8.4. [d] With 60 m*M* butyric acid in 68 m*M* sodium phosphate, and 87 m*M* sodium chloride, pH 6.2. [e] With 24 m*M* octanoic acid in 68 m*M* sodium phosphate and 87 m*M* sodium chloride, pH 6.2. [f] With 4 m*M* dodecanoic acid in 250 m*M* tromethamine, pH 8.4. [g] Significantly different from the control mean ($p < 0.02$).

propylpropionamide suggest that the absorption-enhancing effect of the additives was due to formation of a complex within a lipid barrier (17, 18). The explanation of complex formation was based on the relatively strong complex ($K_{1:1}$ = 12.5 liters/mole) that was formed in isopropyl myristate by the amides and prednisolone. However, dibutyl sulfoxide forms an even stronger complex ($K_{1:1}$ = 50 liters/mole[9]) with prednisolone in isopropyl myristate while hexanol (3) forms a very weak complex ($K_{1:1}$ = 4.2 liters/mole). The lack of correlation between the association constant for complexation in a lipid environment and the absorption-enhancing effect suggests that complexation may not be the explanation for enhanced prednisolone absorption.

Recent reports on membrane permeability indicate that diffusion across membranes is analogous to diffusion across a polymeric sheet rather than to diffusion within a simple liquid (19, 20). Also, the presence

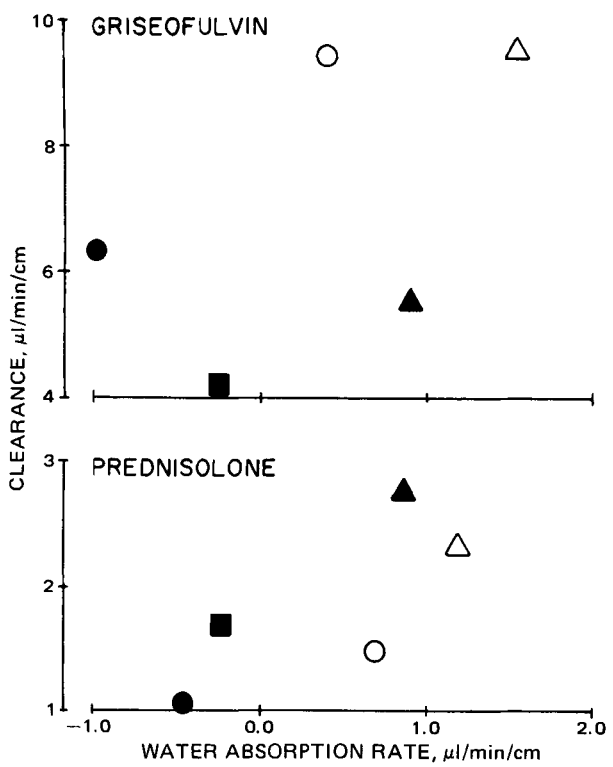

Figure 5—*Clearance of griseofulvin and prednisolone* versus *the water absorption rate. Key:* ○, *68 m*M *sodium phosphate and 87 m*M *sodium chloride, pH 6.2;* ●, *250 m*M *tromethamine, pH 8.4;* △, *60 m*M *butyric acid in 68 m*M *sodium phosphate and 87 m*M *sodium chloride, pH 6.2;* ▲, *24 m*M *octanoic acid in 68 m*M *sodium phosphate and 87 m*M *sodium chloride, pH 6.2; and* ■, *4 m*M *dodecanoic acid in 250 m*M *tromethamine, pH 8.4.*

[9] W. L. Hayton, unpublished data. The phase solubility diagram is curved; analysis of the diagram indicates that two complexes, SL and SL_2, form with association constants of 35 and 4 liters/mole, respectively, at 25°.

Table IV—Effects of Various Additives on the Absorption of Prednisolone and Water from the Perfused Jejunum

Additive[a]	*n*	Intestinal Clearance, % of Control	Water Absorption Rate[b]
Ethanol (3)	4	113	1.98 (0.24)
Butanol (3)	4	123	2.07 (0.71)
Butyric acid	6	154	1.20 (0.30)
Hexanol (3)	5	195	1.98 (0.36)
	4	195	2.26 (0.39)
Dipropylpropionamide (25)	4	171	1.54 (0.23)
Dibutyl sulfoxide[c]	5	170	2.70 (0.70)
Octanoic acid	6	185	0.87 (0.19)
Dodecanoic acid	6	158	−0.23 (0.08)

[a] Reference in parentheses; concentration was approximately 0.5%, except for dodecanoic acid which was 0.08%. [b] Microliters per minute per centimeter of intestine with the standard deviation in parentheses. [c] W. L. Hayton, unpublished data.

of low molecular weight compounds in a membrane, such as general anesthetics, results in an increase in membrane permeability (13). Plasticizers similarly increase the diffusion rate of permeant molecules across synthetic polymeric membranes. It was proposed that plasticizers reduce interchain bonding among polymer molecules, thereby increasing the mobility of permeant molecules within the membrane.

On the basis of differential scanning calorimetry experiments with dipalmitoyllecithin liposomes, it was proposed that compounds such as 1-alkanols, local anesthetics, phenothiazines, and general anesthetics may induce a phase transition in lipid bilayers. The proposed transition is from an organized gel to a randomized liquid crystalline phase (21). When lipophilic small molecules are present, membranes would become more fluid and thinner. It is reasonable to postulate that such changes would also increase membrane permeability. Such a mechanism was proposed to explain the ability of antidiuretic hormone to increase the permeability of the toad urinary bladder to a number of lipophilic solutes (22). Likewise, the effects of temperature on membrane permeability have been attributed in part to a phase transition (23, 24).

A plausible explanation of the effect of the fatty acids on prednisolone absorption is as follows. When the fatty acids are present in the intestinal epithelial cell membranes, they may cause an increase in membrane fluidity and thereby increase the diffusion rate of prednisolone across cell membranes. This explanation accounts for the parabolic relationship

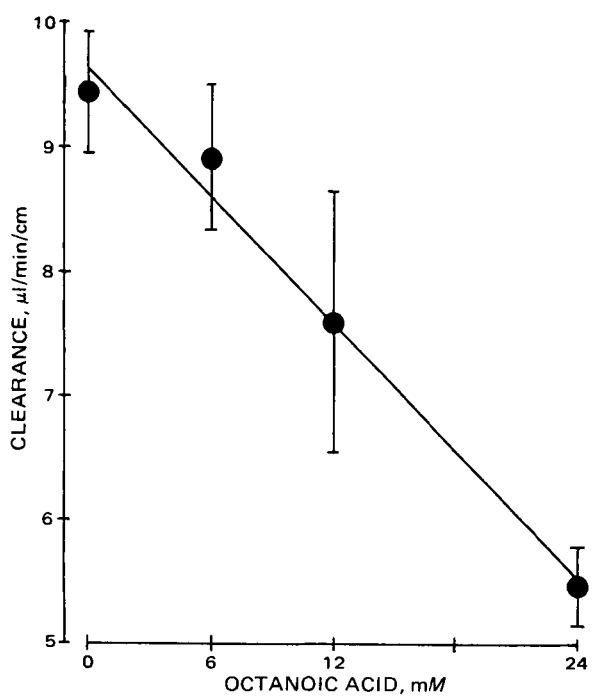

Figure 6—*Effect of various concentrations of octanoic acid on griseofulvin absorption from solutions recirculated through the* in situ *rat jejunum. Each point represents the mean from six experiments, and bars indicate ±1* SE.

between prednisolone clearance and additive concentration (3, 25). Increasing the additive concentration in the perfusate would drive the phase transition to completion, and further increases in the additive concentration would cause proportionately smaller increases in prednisolone clearance. In contrast, the relationship between griseofulvin clearance and additive concentration appears to be linear (Fig. 6), further suggesting that different barriers limit the absorption rate of griseofulvin and prednisolone.

If the effect of the additives listed in Table IV is due to increased membrane fluidity, it may be possible to determine whether the intestinal absorption of any particular compound is rate limited by the cell membranes of the intestinal epithelium. The additives would only increase the absorption rate of those substances whose absorption was membrane rate limited. The effects of one or more of the additives on the absorption of several drugs were observed (3, 17, 18). Prednisolone and closely related prednisone are unique in that they are the only drugs studied whose absorption rate was increased by the additives. Thus, the epithelial cell membrane may not be an important rate-limiting barrier to the absorption of many drugs. *In vitro* and *in situ* studies with rat intestine led to a similar conclusion (26).

In summary, the short and medium chain length fatty acids increase the intestinal absorption rate of prednisolone while they decrease the absorption rate of griseofulvin. The proposed explanation for these effects is that the absorption rate of griseofulvin is limited by the intestinal blood flow rate or an aqueous stagnant layer while the absorption of prednisolone is controlled by the intestinal epithelium. The absorption-altering effects of the fatty acids were attributed to their ability to reduce intestinal blood flow or to increase the thickness of the stagnant layer while simultaneously increasing the permeability of the intestinal epithelium.

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Synthesis and Preliminary Anti-Inflammatory Evaluation of 17β-Amino-3β-methoxy-5-androstene Hydrochloride and Related Derivatives

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Abstract □ To study the anti-inflammatory properties of 17β-aminosteroids, some 17β-aminoandrostene hydrochlorides based on the 3β-methoxy-5-androstene nucleus were prepared. The syntheses were accomplished *via* a two-stage amination of 3β-methoxy-5-androsten-17-one, involving reduction of an intermediate 17-imine or, for the synthesis of 17β-amino-3β-methoxy-5-androstene, the 17-oxime. The compounds were examined for anti-inflammatory activity in the rat cotton pellet model of inflammation. All tested aminosteroids displayed significant activity. Two compounds also were screened in an adjuvant-induced arthritis model of inflammation and displayed activity.

Keyphrases □ 17β-Aminoandrostenes, substituted—synthesized, evaluated for anti-inflammatory activity in rats □ Anti-inflammatory activity—various substituted 17β-aminoandrostenes evaluated in rats □ Structure–activity relationships—various substituted 17β-aminoandrostenes evaluated for anti-inflammatory activity in rats

Over the past two decades, considerable interest has developed in the synthesis and biological evaluation of aminosteroids (1). The compounds produced have various biological properties including antimicrobial, hypocholesterolemic, hypotensive, and local anesthetic.

Anti-inflammatory activity was established for a series of 16β-amino-17α-hydroxy-20-ketopregnenes using the cotton pellet and foot edema models of inflammation (2). The activity associated with these aminosteroids was not influenced markedly by structural alterations that normally enhance the anti-inflammatory activity of corticosteroids.

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