PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 173, 118–124 (1983)

Influence of Dietary Lipids on Intestinal Bile Acid Absorption (41618)

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Abstract. The enterohepatic circulation and the inability of upper small intestine to actively absorb bile acid are physiological adaptations for maintaining adequate bile acid concentrations in the intestinal lumen for use in lipid digestion and absorption. Certain lipids inhibit bile acid absorption suggesting a possible role of lipids in this scheme. Using isolated intestinal villi preparations of hamster ileum, experiments were conducted to assess the degree of inhibition of bile acid absorption by lipids of various classes and to determine the possible mechanism of inhibition. At an initial bile acid concentration of 10.0 m*M*, triolein significantly reduced villus uptake of taurocholic acid by 50% and cholic acid by 38%. This inhibition was similar to the degree of inhibition produced by oleic acid (58 and 48%, respectively). Likewise, representative medium-chain and short-chain triglycerides inhibited taurocholic acid uptake by 35 and 39%, respectively. Results show that triglycerides as well as oleic acid inhibit ileal bile acid uptake. Neither oleic acid nor triolein altered bile acid uptake when micelles were absent from incubation solutions. Furthermore, lipids did not alter absorption of a nonmicelle-forming bile acid, taurodehydrocholic acid. These data imply that dietary lipids in general may inhibit intestinal bile acid absorption. Oleic acid significantly reduced the intermicellar bile acid concentration from 8.9 $\pm$ 0.2 m*M* to 3.9 $\pm$ 0.2 m*M* while tributyrin, tricaprylin, and triolein had no effect. Results from these studies suggest that the mechanism of inhibition appears to be an enhancement of micelle formation. We speculate that this mechanism may be an additional mechanism for maintaining adequate luminal bile acid concentrations and may be the pathophysiologic mechanism contributing to bile acid malabsorption in cystic fibrosis.

The normal digestion and absorption of dietary lipids by the small intestine in mammals is contingent upon the presence of an adequate intraluminal concentration of bile acids (1). Maintenance of this concentration, in turn, depends upon the efficient absorption of the bile acids from the small intestine and their subsequent return to the liver via the portal circulation. The restriction of active bile acid absorption to the distal ileum and the return of bile acids via the enterohepatic circulation have been described as physiological adaptations for the maintenance of optimum bile acid concentration in the proximal small bowel, the site of lipid digestion and absorption (2).

Recent findings from our laboratory suggest that a third mechanism may be involved. We have reported that unhydrolyzed triglyceride inhibits taurocholic acid absorption in the distal small bowel both *in vivo* and *in vitro* (3). This laboratory as well as others have proposed that lipids alter the structure of micelles, presumably by expanding the mixed micelle, thereby reducing the concentration of monomeric bile acid and inhibiting their absorption (3–8).

The inhibition of bile acid absorption by lipids may also have pathophysiologic importance. The presence of mixed micellar solutions in the distal small bowel represents a condition in malabsorptive disease states. Bile acid malabsorption and increased fecal excretion of bile acids have been identified as accompanying disorders of cystic fibrosis (CF) of the pancreas (9). Furthermore, several investigators have proposed that the presence of undigested dietary nutrients in the intestinal lumen of CF patients prevents the normal absorption of bile acids (9–11). As cited earlier, we have reported that only unhydrolyzed long chain triglyceride significantly inhibited taurocholic acid absorption, whereas undigested carbohydrate and protein had no effect on this process (3, 12, 13). These data suggest that only the lipid component of the diet may compromise normal bile acid absorption and thus may be at least partially responsible for the malabsorption reported in CF.

The current study was undertaken to assess

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0037-9727/83 $1.50

the influence of various classes of lipids on the intestinal absorption of bile acids. These studies were performed *in vitro* under conditions representing malabsorption disease states. In this way it could be determined if the effects of these lipids on bile acid absorption play a significant role in maintaining adequate bile acid concentrations in the proximal small bowel. Furthermore, a possible mechanism by which lipids may influence bile acid absorption is explored and the relationship of these findings to bile acid malabsorption in CF is proposed.

Materials and Methods. Taurodehydrocholic acid (TDH) was purchased from Calbiochem, La Jolla, California. All other nonradioactive compounds used in this study were purchased from Sigma Chemical Company, St. Louis, Missouri. All radioactive compounds, [^{3}H]cholic acid, [^{3}H]taurocholic acid, and [^{14}C]taurine were purchased from New England Nuclear, Boston, Massachusetts. Using the [^{14}C]taurine, [^{14}C]TDH was graciously prepared for us by Dr. Leon Lack of Duke University according to a procedure previously described (14). Krebs–Ringer bicarbonate (KRB) at pH 7.4 was the physiologic solution used throughout this study. Bile acid absorption rate was determined in all studies from incubation solutions containing initial bile acid concentrations of either 0.1 or 10.0 m*M*. When lipids were included, the total amount of a specific lipid in the incubation medium was equal to the amount (in milligrams) of bile acid present at 0.1 or 10.0 m*M*. Therefore for every lipid tested, the ratio of lipid to bile acid in the incubation medium was 1:1 (w/w). Since triglycerides are not solubilized by bile acids, the lipid-containing solutions were sonicated for 15 min to produce a homogeneous microemulsion that remained stable throughout the experiment. All solutions were maintained at 37°C.

Male golden hamsters, 140–150 g (Engel, Farmersburg, Ind.) were used throughout this study. All animals were housed in the institutional animal facility and provided with standard laboratory chow and tap water. Prior to each experiment, animals were fasted for 24 hr with water allowed *ad libitum*.

Intestinal bile acid absorption and the effects of various lipids on this process were examined *in vitro* using the villus technique (15). Following ether anesthesia and midline laparotomy, the ileal portion of the hamster small bowel was isolated and full thickness antimesenteric discs (5–8 mm diameter) of terminal ileum were taken and placed in an oxygenated holding bath of KRB. No more than five tissue samples were taken from each animal. After the transfer of one piece of tissue to each incubation vessel (containing 4.9 ml of KRB) and an equilibration period of 30 sec at 37°C, 100 μl of a concentrated stock solution of bile acid, with appropriate radiolabeled tracer, was pipetted into the vessel. Lipids were included where appropriate. All tissue samples were incubated for 1 min at 37°C with constant shaking at 140 cycles/min in an atmosphere of humidified 5% CO_2 in O_2. Tissue samples were then retrieved, rinsed, quickly frozen in KRB, and lyophilized overnight. Following removal of the villi, the remaining tissue, as well as the villi, were solubilized separately and radioactivity in all tissues and incubation media were determined with a Beckman model LS-333 liquid scintillation counter. Specific activity in counts per minute per micromole of each incubation media was determined from standards run concurrently. The uptake rate of bile acid *in vitro* was calculated as [cpm (villi) ÷ specific activity] ÷ tissue wt (grams) and expressed as micromoles per gram (dry wt) per minute. Using [^{3}H]inulin we have previously determined the distribution of extracellular space in this preparation to be negligible (0.1%) (16). Therefore in subsequent experiments the inulin marker was not utilized.

Initial experiments were performed to compare the effects of triolein and oleic acid on the uptake of TCA and CA by villi of hamster ileum. Studies were then conducted to assess the influence of representative triglycerides on the uptake of TCA and TDH in this system. Finally, using [^{3}H]TCA and the equilibrium dialysis method of Duane (17), the effect of the three triglycerides and oleic acid on the intermicellar bile acid concentration (IMBC) was examined. Since temperature ranging from 20–40°C has negligible effect on most bile acid micelles (18), dialyses were done at room temperature with constant stirring for 24 hr. Dialysis tubing (Spectrum Medical) having a minimum molecular weight retention of 12,000 was used throughout. All samples were adjusted to pH 7.5 ± 0.3 with 1 *M* NaOH or HCl as previously described (17).

A 2-ml aliquot of simple or mixed micelle solution (containing tracer of known specific activity) was loaded into the dialysis tubing and dialyzed against 10 volumes of 0.1 *M* NaCl. Radioactivity in 0.5-ml aliquots of dialysate and retentate was determined as above and appropriate calculation of IMBC was made.

The significance of alterations in bile acid absorption was determined using randomized block analysis of variance. Significant changes in IMBC were determined using the paired *t* test. Significant differences were accepted at a *P* value of less than 0.05 in all studies.

Results. The first series of experiments were designed to demonstrate the effects of triolein (TO), a common long-chain dietary triglyceride and oleic acid (OA), a common end product of lipid hydrolysis in the intestine, on the uptake of taurocholic (TCA) and cholic (CA) acid by isolated ileal villi of the hamster. These results are presented in Table I. At initial TCA and CA concentrations of 0.1 m*M*, TO and OA did not alter the uptake rate of either bile acid by ileal villi. However, at a bile acid concentration of 10.0 m*M*, OA significantly reduced the mean villus uptake of TCA by 58% and of CA by 48%. Likewise, TO significantly inhibited the mean uptake of TCA and CA by 50 and 26%, respectively.

The next series of experiments were conducted to determine the influence of triglycerides of various chain lengths on intestinal bile acid uptake *in vitro*. Representative short-, medium-, and long-chain triglycerides were introduced into the TCA incubation medium. Results shown in Fig. 1 indicate that tributyrin (TB), a short-chain triglyceride, significantly reduced TCA absorption by 39%.

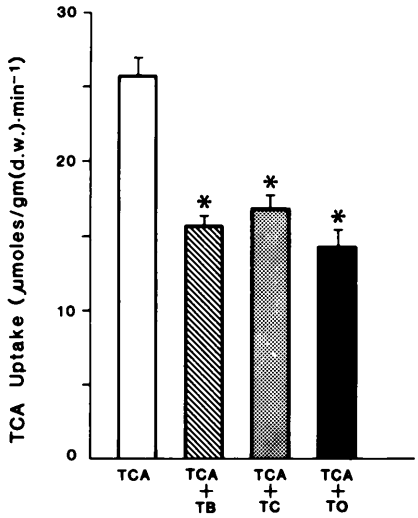

FIG. 1. Uptake rate of TCA by villi isolated from hamster ileum and the effect of tributyrin (TB), tricaprylin (TC), and triolein (TO) on this process. Tissue was incubated and analyzed as described in Methods. Bars represent mean ± SEM for 12 samples in each group. *, Significantly different from control to at least the 0.05 level.

Also, a medium-chain triglyceride, tricaprylin (TC), significantly inhibited TCA uptake (34%). Likewise, TO markedly reduced TCA uptake (44%), as in the first series of experiments and when studied in parallel experiments with the other triglycerides.

In the third series of experiments, the effects of the triglycerides of various chain lengths on the uptake of TDH was assessed. This bile acid has been shown to be actively transported by the ileal mucosa (19) and is of particular interest because it does not form bile acid micelles. Therefore, any effect on the absorption of this bile acid would suggest an

TABLE I. EFFECT OF TRIOLEIN AND OLEIC ACID ON TAUROCHOLIC AND CHOLIC ACID UPTAKE BY VILLI ISOLATED FROM HAMSTER ILEUM

	TCA uptake μmole/g (dry wt)·min⁻¹		CA uptake μmole/g (dry wt)·min⁻¹	
	0.1 m*M*[a]	10.0 m*M*[a]	0.1 m*M*[a]	10.0 m*M*[a]
Control	3.29 ± 0.44 (6)	27.9 ± 3.1 (10)	2.47 ± 0.22 (6)	31.2 ± 1.6 (10)
TO added	3.35 ± 0.44 (6)	13.9 ± 0.9* (8)	2.48 ± 0.30 (6)	19.2 ± 0.9* (8)
OA added	3.17 ± 0.41 (6)	11.7 ± 0.6* (8)	2.25 ± 0.26 (6)	16.1 ± 1.1* (8)

Note. Values are expressed as the mean ± SEM for the number of experiments indicated within the parentheses. The asterisk indicates the value for uptake was significantly different from control to at least the 0.05 level according to analysis of variance.

[a] The initial bile acid ($[BA]_i$) concentration.

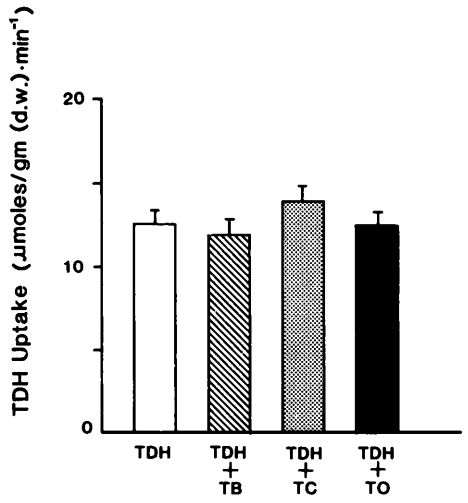

FIG. 2. Uptake rate of TDH by villi isolated from hamster ileum and the effect of TB, TC, and TO on this process. Tissue was incubated and analyzed as described in Methods. Bars represent mean ± SEM for 16 samples in each group.

interaction of the lipid with only the monomeric form of the sterol. The results shown in Fig. 2 indicate that none of the lipids tested significantly altered the villus uptake of TDH.

The effects of these lipids on intermicellar bile acid concentration (IMBC) was tested using the method of Duane (17). The results of these studies are shown in Table II. The addition of TB, TC, and TO to 10.0 m*M* TCA did not alter the IMBC from control in all cases. However, addition of OA, which is known to expand micelles (20), to the TCA solution, dramatically reduced the IMBC. With OA, the IMBC was reduced 56% from control (TCA alone).

Discussion. The present study was undertaken to determine the degree of influence of representative lipids on bile acid absorption by the hamster ileum *in vitro*. Experiments were also carried out to differentiate by what mechanism these lipids influence this physiological process and what possible relationship exists between this mechanism and bile acid malabsorption in cystic fibrosis.

The results of the present study show that triolein significantly inhibits villus uptake of TCA at 10.0 m*M* and confirm our earlier finding that unhydrolyzed triglyceride reduces TCA absorption both *in vitro* and *in vivo* (3). This finding however is in conflict with those of Roy *et al.* (21) and Harries *et al.* (22) who have shown that triolein had no effect on the ileal absorption of TCA in the rat *in vivo*. Whereas the variation in techniques, animals species, and concentrations used could account for the discrepancy between the findings of our study and those of others (21, 22), results from our previous *in vivo* studies (3) and the additional finding here that triolein also inhibits the villus uptake of unconjugated cholic acid (CA) support our original conclusion that unhydrolyzed triglyceride compromises normal bile acid absorption by the ileum. This effect was not observed when the bile acids were present in low concentration (0.1 m*M*). It would be of interest to note whether a dose-response relationship exists between bile acid uptake and triglycerides. From previous work we have shown this type of relationship does not exist between bile acid uptake and phospholipid (4).

In addition, this study supports the finding (8, 21, 23) that oleic acid, a common endproduct of triglyceride hydrolysis, also significantly reduces the villus uptake of both TCA and CA. Again this inhibition was seen only when the bile acid concentration was 10.0 m*M* (Table I). Since both a fatty acid and a triglyceride inhibit uptake of bile acids, we speculate that partial endproducts of triglyceride digestion, i.e., mono- and diglycerides, may

TABLE II. THE INTERMICELLAR BILE ACID CONCENTRATION (IMBC) OF VARIOUS TCA–LIPID SOLUTIONS AS DETERMINED BY EQUILIBRIUM DIALYSIS

	TCA alone	TCA + TB	TCA + TC	TCA + TO	TCA + OA
IMBC	8.9 ± 0.2	9.0 ± 0.03	9.1 ± 0.01	9.0 ± 0.01	3.9* ± 0.2

Note. Values are expressed as the mean TCA concentration in mmole/liter of four experiments. The asterisk indicates that the value is significantly different from TCA alone at the $P < 0.001$ level according to the Student's t test. The IMBC consists of simple micellar bile acid plus monomeric bile acid. See text for other abbreviations.

have, by different mechanisms, a similar effect on intestinal bile acid uptake, although this was not examined here. Roy *et al.* (21) reported a reduction of TCA absorption *in vivo* when monoolein was included in the luminal fluid. However, in those studies, the luminal fluid also contained oleic acid. As with triolein, oleic acid had no affect on villus uptake of TCA or CA when these bile acids were present at 0.1 m*M*.

We have also shown that different triglycerides inhibit TCA uptake (Fig. 1). These studies suggest that perhaps all unhydrolyzed triglycerides reduce normal intestinal bile acid absorption. Preliminary results from our laboratory suggest that these three triglycerides also inhibit the uptake of the glycine conjugate of cholic acid. Medium-chain triglyceride-containing diets have been proposed by some to alleviate fat malabsorption in cystic fibrosis (CF). Kuo and Juang (24) found that alteration of the diet of CF patients to include medium-chain triglyceride reduced steatorrhea and improved the rate of weight gain in these patients. While this approach may reduce to some extent the problem of fat malabsorption often seen in CF, our results would suggest that malabsorption of bile acid would remain a problem. Thus, while fecal fat excretion may be reduced by treatment with medium-chain triglyceride, intraluminal lipid digestion and absorption would continue to be partially inhibited due to a reduced bile acid pool. Thus, the total nutritional status of these patients would still be compromised.

A possible explanation of reduced bile acid absorption in the presence of lipids is the involvement of the unstirred water layer adjacent to the intestinal mucosa. Under experimental conditions, it has been shown that intestinal uptake of bile acids from micellar solutions is rate-limited by diffusion through the unstirred water layer (8). One can visualize a reduced rate of diffusion of bile acids through the microemulsion used in these studies resulting in reduced bile acid concentration at the absorptive site on the brush border membrane. It is assumed however that since all of these studies were conducted under identical experimental conditions (i.e., constant shaking at 140 cycles/min) the unstirred water layer had little influence on these results.

The mechanism by which triglycerides alter bile acid absorption is unknown. We have previously suggested that perhaps these lipids expand the size of micelles, thus reducing monomeric bile acid molecules available for absorption (3, 4). From the work of Carey and Small (20), it is generally well accepted that triglycerides partition poorly into bile acid micelles and therefore are unlikely candidates as agents to cause micellar swelling. However, as reported in the present study, when TCA and CA absorption is measured at 0.1 m*M* (presumably when no micelles are present) triglyceride does not alter absorption rates. Also, taurodehydrocholic acid (TDH) is a bile acid with an aggregate number of 1 (18) thus does not form micelles and when uptake of this bile acid is measured, triglyceride had no adverse effects. We have reported that phospholipid has no effect on TCA or CA absorption at concentrations below the critical micellar concentration (CMC) (4). Likewise, in this study we have shown neither triolein nor oleic acid alters uptake of TCA or CA when these bile acids are present at 0.1 m*M* and presumably no micelles are present. Therefore, the effect of triglyceride on bile acid absorption is only seen when micelles are present, suggesting that these lipids reduce the monomeric bile acid available for absorption by altering either the formation or the size of micelles, without partitioning into them.

Alteration of micellar size was investigated using the equilibrium dialysis method (17) for measuring the intermicellar bile acid concentration (IMBC). The IMBC is comprised of bile acid monomers and simple micelles, both of which are small enough to dialyze. Any larger micelles or mixed micelles are retained by the dialysis membrane. As shown in Table II, representative triglycerides do not alter the IMBC as did oleic acid which is known to expand micelles (18). Thus, triglyceride does not reduce monomeric bile acid concentration by enlarging micelles. It may be that these triglycerides increase micelle formation by shifting the micelle–monomer equilibrium to the micelle phase perhaps via reduction of the CMC of bile acids. This hypothesis is plausible but remains untested (18, 20), although other lipids are known to reduce bile acid CMC (20). One can envisage that increasing micelle formation would reduce the mono-

meric bile acid concentration. This would account for the results seen with the equilibrium dialysis studies (i.e., no change in IMBC) while explaining the adverse effect of triglycerides on intestinal bile acid uptake since bile acids are only absorbed in the monomeric form (6, 25).

The results of this study may have significant physiological implications in the overall understanding of bile acid–lipid interaction in the intestinal lumen following a meal. Bile acids are absorbed solely by passive diffusion throughout most of the small bowel, while a highly efficient sodium-dependent active transport mechanism exists in the terminal ileum (26). This absorption pattern has been described as a physiological adaptation for maintaining optimal concentrations of bile acids in the proximal small bowel to insure normal digestion and absorption of dietary lipids (2). At concentrations used in this study (i.e., 10 m*M*), the bile acid molecules will aggregate and, together with some lipolytic end products form mixed micelles, while yet unhydrolyzed triglycerides could increase micelle formation by lowering the CMC. Since bile acids are absorbed only in monomeric form (6, 25), the increase in micelle size and formation produced by intraluminal lipids reduces the bile acid absorption in the upper small bowel. As food moves down the intestine, lipolysis continues, the end products of which are absorbed, thereby reducing micellar size and number. As micelles become smaller and approach the simple micelle stage, there is an increase in the concentration of monomeric bile acid available for absorption. As more lipid and bile acid are absorbed, the equilibrium between micellar and monomeric bile acid continues to shift to the monomer phase. Coincident with the intraluminal lipid concentration approaching a minimum in the ileum, the more efficient bile acid absorptive mechanisms are encountered and monomeric bile acid is now actively absorbed by the ileal mucosa (27). Considered within this scenario, our present results suggest that increased micelle formation induced by triglycerides in the upper small bowel is an additional mechanism for the maintenance of adequate bile acid concentrations in this area of the intestine.

This mechanism of inhibition may have clinical as well as physiological significance. This laboratory has earlier proposed that pancreatic insufficiency in CF may initiate an intraluminal event involving unhydrolyzed lipids which results in the observed bile acid malabsorption in this disease (3). Increased micelle formation by unhydrolyzed lipids may inhibit normal bile acid absorption by the CF small intestine. While more recent work indicates that intestinal malabsorption of bile acids in CF results at least in part from a primary ileal mucosa cell defect (16), increased micelle formation by unhydrolyzed lipids may be a contributing factor responsible for this clinical finding.

In conclusion, it has been shown that triglycerides as well as fatty acids inhibit bile acid uptake by ileal villi of the hamster. In addition, triglycerides representative of the three major classes all reduce bile acid uptake. These results indicate that perhaps most, if not all, dietary forms of lipid inhibit intestinal bile acid absorption and may contribute to the bile acid malabsorption seen in CF of the pancreas. Furthermore, the mechanisms by which these lipids influence this process are different. Lipolytic end products expand mixed micelles whereas unhydrolyzed triglycerides may increase micelle formation reducing monomeric bile acid concentration. We suggest that this latter mechanism has physiological significance in the normal intestinal digestion and absorption of lipids and clinical importance in the pathophysiology of bile acid malabsorption in cystic fibrosis.

The author expresses his sincere thanks to Dr. Leon Lack for the preparation of [^{14}C]TDH used in this study and to Dr. Douglas K. Anderson for this helpful review of this manuscript. The author also acknowledges the technical assistance of Jennifer Pollock and Terry Madden and the secretarial assistance of Rhonda Jacobs. This study was supported by grants from the National Institutes of Health (AM-26650) and from the Cystic Fibrosis Foundation.

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Received October 6, 1982. P.S.E.B.M. 1983, Vol. 173.