

Comparative effects of cholic, chenodeoxycholic, and ursodeoxycholic acids on micellar solubilization and intestinal absorption of cholesterol

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Abstract Cholesterol absorption was studied in mice receiving cholic, chenodeoxycholic, or ursodeoxycholic acids (0.2% of the diet) for 2 months. Cholesterol absorption was greater with cholic acid (79%) than with chenodeoxycholic acid feeding (60%) and the lowest levels were observed during ursodeoxycholic acid feeding (37%). Under the three diets, bile acid pool and bile acid secretion were not different. Biliary cholesterol secretion was increased by cholic acid. The bile acid fed represents at least 80% of total bile acids. Micellar solubilization of oleic acid and cholesterol in the presence of each tauro-conjugated bile salt (10 mM) was determined in vitro by the coprecipitation method. Whatever the pH conditions, taurochenodeoxycholate solubilized significantly more cholesterol and more oleic acid than taurocholate. Tauroursodeoxycholate had the poorest detergent properties for both lipids. The differences between the three bile salts for cholesterol solubilization were enlarged by lowering pH and by high oleic acid concentration. Therefore the decrease in cholesterol absorption observed during ursodeoxycholic acid feeding could be explained by the poor detergent properties of this bile salt species. On the other hand, there is no relationship between the detergent properties of taurochenodeoxycholate and taurocholate and their effects on cholesterol absorption in mice. These results suggest that, in this particular case, micellar solubilization is not the rate limiting step in cholesterol absorption.—**Reynier, M. O., J. C. Montet, A. Gerolami, C. Marteau, C. Crotte, A. M. Montet, and S. Mathieu.** Comparative effects of cholic, chenodeoxycholic, and ursodeoxycholic acids on micellar solubilization and intestinal absorption of cholesterol. *J. Lipid Res.* 1981. **22**: 467–473.

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In spite of conflicting results in man (1–3), various works have shown that, generally, dihydroxy bile acids are less effective than cholic acid in the promotion of cholesterol absorption (4–6). This difference is often attributed to a specific effect of cholic acid on intestinal

cholesterol esterase, an effect not shared by other bile acids (7, 8). However other explanations have not been ruled out. In particular, the role of specific effects of bile acids on intraluminal cholesterol solubilization must be considered. Mixed micelle formation could be modified during bile acid feeding by two mechanisms. First, it has been shown that ursodeoxycholate and its conjugates solubilize much less cholesterol than the other bile salts both in the presence of lecithin (9) and of monoolein-fatty acid mixtures (10). There is no large difference between the solubilizing capacities of cholate and chenodeoxycholate (10, 11) but these results were obtained using total lipid concentrations largely exceeding those observed during fat digestion. Second solubilization depends on the bile acid pool which may be differently modified by each molecular species of bile acid.

This work was designed to compare the effects of ursodeoxycholic, chenodeoxycholic, and cholic acids on cholesterol absorption and on biliary secretion in mice and, in vitro, on cholesterol solubilization in bile salt-oleic acid micelles.

MATERIALS AND METHODS

Treatment of animals

Swiss female mice, weighing 22 to 25 g, were divided into four groups and fed one of the following diets: *a*) chow diet, *b*) chow diet supplemented with 0.2% cholic acid, *c*) chow diet plus chenodeoxycholic acid (0.2%), *d*) chow diet plus ursodeoxycholic acid (0.2%). The amount of bile acid fed was therefore about 500 mg/kg per day. Two months later, bile secretion or intestinal absorption of cholesterol were studied.

In some animals histological examinations of the small intestine were performed. Intestinal transit time was studied in three mice of each group using carmine red as marker.

Cholesterol absorption

Intestinal absorption of cholesterol was determined by two methods. The first was the dual isotope ratio method of Zilversmit (12) which measures intestinal absorption of a single dose of cholesterol. After a 15-hr fast, each mouse received by intubation 9.2 μmol of cholesterol containing 0.5 μCi of [^{14}C]-cholesterol emulsified with albumin and oleate (40 μmol). At the same time they received a colloidal suspension of 1 μCi of [^3H]-cholesterol intravenously. Feces were collected daily for 3 days to measure the fecal radioactivity in the neutral sterol fraction. The ratio of the specific radioactivities (^3H and ^{14}C) of blood cholesterol was calculated 72 hr after intubation. Blood samples were first weighed, then completely oxidized in an Intertechnique Oxymat apparatus J.A. 101 before determining the radioactivity content.

The second method was the sterol balance method measured isotopically (13). By this method, cholesterol absorption (exogenous cholesterol) is obtained from the determination of the unabsorbed dietary cholesterol = daily fecal total neutral steroids (minus fecal plant sterols) minus endogenous neutral steroids. Cholesterol and plant sterols were determined by gas-liquid chromatography. The daily endogenous neutral sterols were estimated isotopically (after injecting [^{14}C]-cholesterol) by dividing the radioactivity present in fecal sterols by the specific activity of plasma cholesterol. Mice received [^{14}C]-cholesterol (1 μCi intravenously). Three weeks later, stools were collected for four periods of 4 days. The mean plasma cholesterol radioactivity of the 2 first days of each period was used for the calculations.

Bile secretion

Biliary secretion was studied in animals with a complete biliary fistula placed 2 hr after they received an emulsion of oleate, cholesterol, and albumin. Hourly secretion of bile salts, lecithin, and cholesterol was measured. The bile acid pool was calculated from the total bile salt secretion of the first 10 hr of biliary drainage, from which basal secretion observed after this time was then subtracted.

In vitro study of lipid solubilization

The micellar solubilization of lipids in bile salt solution was studied by the coprecipitation method (10, 11). The appropriate amounts of bile salt and oleate were dissolved in organic solvents. The solvent was evap-

orated in vacuo over phosphorus pentoxide for 24 hr, then the dried mixtures were dissolved in phosphate buffer, pH = 6.2 or 6.7, 0.14 M Na^+ at 37°C so that each mixture had a concentration of 10 mM of bile salt. The maximum solubility of the oleic-oleate compounds was estimated by turbidimetry. Cholesterol solubilization was measured at three molar ratios of bile salt to oleate. Bile salt concentration was kept constant (10 mM) and oleate concentrations were, respectively, 3.9 mM, 6.2 mM, 9.3 mM for pH = 6.7, and 3.9 mM for pH = 6.2. Various amounts of cholesterol were added to obtain mixtures with a fixed ratio of bile salt to oleate and increasing amounts of cholesterol. To obtain equilibrium cholesterol solubility at 37°C, solutions containing 4 g/dl of lipids were first prepared, heated to 80°C for a few minutes, cooled at 37°C, and then diluted with phosphate buffer containing 0.14 M Na^+ in order to reach a final bile salt concentration of 10 mM. The changes in the physical state of the supersaturated solutions were followed for 8 days. Cholesterol equilibrium values were generally obtained on the 5th day. The separation of a second phase (cholesterol crystals, paracrystalline phases) from the isotropic solutions was monitored by optical methods: polarizing microscope and scattered light. Turbidity measurements were obtained with a Brice Phoenix light-scattering apparatus, model 2000, with a light wavelength of 546 nm. The scattered light intensity was measured at angles of 0° and 90°.

The solubility values reported are average values of at least three separate determinations. Individual measurements did not deviate more than 5% from the average.

Analytical methods

Total bile acids in bile were measured with an enzymatic technique using 3 α -hydroxysteroid dehydrogenase (Worthington Biochemical Corporation) (14). Individual bile acids were analyzed by gas-liquid chromatography; after saponification of bile (1.25 N NaOH, 2 hr at 110°C), bile acids were converted to their methyl esters with diazomethane and acetylated with trifluoroacetic anhydride. Bile acid derivatives were dissolved in chloroform and injected in a Tracor MT 220 gas chromatograph equipped with a hydrogen flame ionization detector. Two-meter U-tubes, 4 mm i.d., were packed with QF₁ (0.3%) on Gas Chrom Q, 100–120 mesh (coating and support from Applied Science Laboratories, State College, PA). Nitrogen was used as carrier gas and column temperature was 220°C.

Conjugated bile acids were estimated from thin-layer chromatography (15) and taurine determination

after acid hydrolysis (5.6 N HCl, 18 hr at 110°C in vacuo with a Jeol amino acid analyzer model JLC 5 AH).

Neutral sterols were extracted from feces by the method of Folch, Lees, and Sloane Stanley (16). Neutral sterols were measured by the cholesterol oxidase method (17). Trifluoroacetyl derivatives of neutral sterol were separated by gas-liquid chromatography. The same packed column mentioned above was used and column temperature was 190°C. Corrections were made from gas-liquid chromatography for plant sterols and for keto derivatives which were always less than 7% of total fecal sterols. Phospholipids were measured with a colorimetric method (18).

Materials

Chow diet from Villemoisson, France contained 0.02% of cholesterol (6 $\mu\text{mol}/10\text{ g}$). Ursodeoxycholic acid was a gift from Doctor H. Falk. Chenodeoxycholic acid was a gift from Roussel laboratories. Other products were of the A grade: cholesterol, sodium oleate (Sigma), sodium taurocholate, taurochenodeoxycholate, and tauroursodeoxycholate (Calbiochem). [4- ^{14}C]Cholesterol (40–50 $\text{mCi}\cdot\text{mmol}^{-1}$ was 98% pure (CEA, France). [^3H]Cholesterol (0.3–0.5 $\text{Ci}\cdot\text{mmol}^{-1}$) from CEA, France was found to be greater than 90% pure. Radioactivity measurements were made using an Intertechnique liquid scintillation system SL40.

Statistical analysis

The results are expressed as mean values and standard deviation of the means. Student's *t* test was used to determine statistical significance.

RESULTS

Intestinal Absorption of Cholesterol

Cholesterol absorption depends on the composition of the diet (Table 1). In the two conditions studied, acute administration of cholesterol or daily absorption of cholesterol from the diet, similar results were obtained. The amount of cholesterol absorbed was larger with cholic acid (79%) than with chenodeoxycholic acid (60%) and much greater than with ursodeoxycholic acid (37%). However, the values of cholesterol absorption were not significantly different for cholic acid or chenodeoxycholic acid diets compared to the chow diet. Only ursodeoxycholic acid decreased cholesterol absorption compared to controls (2 $P < 0.05$). The absolute amounts of cholesterol absorbed were evidently different after the acute oral

administration of 9.2 μmol of cholesterol compared to those obtained with chronic administration (between 5 to 6 μmol brought daily by the diet). In the two circumstances, the percent of cholesterol absorption was comparable, respectively 80 and 77% with cholic acid, 60 and 59% with chenodeoxycholic acid, and 44% and 27% with ursodeoxycholic acid. Histological studies of jejunum, after 4 months of bile acid feeding, did not show any abnormality. Microvilli appeared normal by electron microscopy.

Intestinal transit time, measured after carmine red intubation, was identical in all groups studied. The dye appeared in stools during the second hour following ingestion and fecal excretion lasted 24 hr in the four groups. Furthermore, fecal excretion of [^{14}C]cholesterol, given in experiments using the Zilvermit method, was followed daily. $78.8\% \pm 5.4$ of the unabsorbed cholesterol was recovered the first 24 hr and $15.9\% \pm 3.4$ during the following day in controls. The corresponding values were $75.7\% \pm 5.6$ and $19.9\% \pm 6.5$ under cholic acid, $84.8\% \pm 2.0$ and $11.6\% \pm 2.4$ under chenodeoxycholic acid, and $79.5\% \pm 3.0$ and $12.0\% \pm 3.2$ under ursodeoxycholic acid.

Biliary secretion

Addition of bile acids to the diet increased the bile salt pool and biliary secretion of bile salts compared to controls during the first hour (2 $P < 0.05$) (Table 2). However we did not note any differential effect of the three bile salts on these two parameters. In all cases, from the comparison of taurine determination and the enzymatic assays of bile salts, we showed that 80–90% of the bile salts were tauroconjugated with a non-sulfated $3\alpha\text{OH}$. On the contrary, the bile acid composition of bile was markedly modified, the administered bile acid becoming the predominant biliary bile acid. The biliary secretion was slightly increased by ursodeoxycholic acid or chenodeoxycholic acid but the difference with controls did not reach statistical significance. Cholic acid feeding induced a higher secretion of cholesterol than the two other bile acids for the same bile acid output (2 $P < 0.05$). Lecithin secretion in all cases paralleled bile acid secretion.

In vitro studies

Solubility of oleic acid in bile salt solutions. In 10 mM solutions, bile salts dispersed the fatty acid into micellar solutions with different abilities (Table 3). As in other studies (9, 10), tauroursodeoxycholate was shown to be a poor detergent. We observed also a small but clear difference between the dissolving powers of taurocholate and taurochenodeoxycholate

TABLE 1. Intestinal absorption of cholesterol

Diet	Acute Administration			Chronic Administration	
	Dual Isotope Method	Fecal Recovery Method	Absorption	Balance Method	Absorption
	μmol	μmol	molar %	$\mu\text{mol/day}$	molar %
Controls	6.27 \pm 0.63 (5)	6.13 \pm 0.54 (9)	67.2	3.92 \pm 0.40 (7)	65.0
Chenodeoxycholic acid	5.38 \pm 0.31 (5)	5.63 \pm 0.48 (7)	60.1	3.12 \pm 0.32 (7)	59.0
Cholic acid	7.31 \pm 0.49 (5) ^b	7.38 \pm 0.37 (9) ^b	80.0	4.60 \pm 0.60 (7) ^b	77.1
Ursodeoxycholic acid	3.77 \pm 0.63 (5) ^{a,b}	4.20 \pm 0.41 (6) ^{a,b}	43.6	1.68 \pm 0.54 (7) ^{a,b}	27.2

^a Significantly different from controls ($2P < 0.05$).

^b Significantly different from chenodeoxycholic acid ($2P < 0.05$).

Acute administration of cholesterol consisted of 9.2 μmol of cholesterol mixed with 40 μmol oleate. The daily cholesterol intake was 6.03 μmol for controls, 5.29 μmol for chenodeoxycholic acid, 5.97 μmol for cholic acid, and 5.88 μmol for ursodeoxycholic acid diets. Values represent the mean \pm S.D. Numbers of animals is indicated in parentheses.

which was not observed in more concentrated solutions for lecithin or oleate. At a bulk pH = 6.7, oleic acid is about half-ionized when present in a bile salt micelle (19). The decrease in the degree of ionization at pH 6.2 is followed by an enlargement of the differences between the three bile salts, with a particularly dramatic decrease in the solubilization power of tauroursodeoxycholate.

Cholesterol solubility. As observed for oleic acid, the equilibrium solubility of cholesterol depends very much on the bile salt species (Table 4). The distinct capacities of the bile salts were more apparent when the fatty acid concentration was increased. With 6.2 mM oleic acid, the solubility of cholesterol was extremely low in tauroursodeoxycholate solution although this fatty acid concentration was far from the solubility limit of oleic acid (7.86 mM).

The effects of pH were tested for solutions containing 3.9 mM oleic acid. At pH 6.2, cholesterol solubility was 0.60 mM with taurochenodeoxycholate, 0.26 mM with taurocholate, and not measurable with tauroursodeoxycholate.

DISCUSSION

Cholesterol absorption

This work shows that, in mice, the three bile acids exert very different effects on cholesterol absorption. The decreased absorption observed with ursodeoxycholic acid feeding confirms earlier studies in other species including man (6, 20). It is more marked during the balance studies than during administration of a single large dose of cholesterol. This may result from an increased secretion of endogenous cholesterol without prior equilibration with the rapidly exchanging pool of cholesterol, giving an overestimation of non-absorbed cholesterol by the sterol balance method. The difference between the effects of cholic acid and chenodeoxycholic acid administration has also been observed earlier in the rat, during tauroderivative administration (5). The situation is more confusing in man (2): recent results show no change in cholesterol absorption during cholic acid feeding (3) and no change (2) or a decrease (1) during cheno-

TABLE 2. Comparative effects of the diets on bile secretion

Diet	Number of Mice	Bile Acid Pool Size	Bile Acid Composition			Lipid Composition during the First Hour		
			CA	CDCA	UDCA	Bile Acids	Cholesterol	Phospholipids
			μmol	molar%		$\mu\text{mol/hour}$		
Controls	5	10.25 \pm 1.10	62 \pm 6	21 \pm 4	0	2.60 \pm 0.40	0.17 \pm 0.07	0.57 \pm 0.06
CDCA	5	19.27 \pm 3.10 ^a	11 \pm 2	86 \pm 3	0	4.41 \pm 0.71 ^a	0.24 \pm 0.02	0.79 \pm 0.23
CA	5	26.14 \pm 3.83 ^a	91 \pm 5	3 \pm 1	0	5.21 \pm 0.90 ^a	0.79 \pm 0.79 ^{a,b,c}	0.80 \pm 0.10
UDCA	5	23.35 \pm 1.85 ^a	8 \pm 3	11 \pm 2	80 \pm 3	4.80 \pm 0.83 ^a	0.23 \pm 0.07	0.78 \pm 0.11

^a Significantly different from controls ($2P < 0.05$).

^b Significantly different from chenodeoxycholic acid diet ($2P < 0.05$).

^c Significantly different from ursodeoxycholic acid diet ($2P < 0.05$).

CDCA, chenodeoxycholic acid; CA, cholic acid; UDCA, ursodeoxycholic acid.

deoxycholic acid administration. In the present study, the difference between cholic acid and control diets did not reach statistical significance. However, one must take into account that, in cholic acid-fed mice there is a marked increase in biliary cholesterol secretion that is absorbed at least to the same extent as dietary cholesterol (21). We may then conclude that, in mice, cholic acid feeding actually increases cholesterol absorption.

The differences observed between the effects of the three bile acids do not seem secondary to general modifications of intestinal absorption: histologic examinations did not show any toxic effect of chenodeoxycholic or ursodeoxycholic acid treatment on intestinal mucosa. Intestinal transit time, which may influence cholesterol absorption (22), was similar whatever the bile acid fed, as shown from the rate of excretion of unabsorbed cholesterol and the carmine red studies.

Therefore, the results depend on the distinct effects of the bile salts on specific steps of cholesterol absorption. In our acute studies, cholesterol was given in its nonesterified form with oleate, and micelle formation may occur without prior hydrolysis. The results must be due to modifications of micellar transport and/or to specific influences on intramucosal steps of cholesterol absorption. Indeed, it has been shown that taurocholate increases intramucosal cholesteryl ester formation more than taurochenodeoxycholate (7, 8); this may increase the rate of cholesterol absorption. However, the importance of this effect in controlling cholesterol absorption is unknown, and its existence does not exclude another possible specific action of various bile salts on micellar solubilization of cholesterol. Bile acid-containing diets may influence two parameters governing mixed micelle formation: bile salt enterohepatic circulation and bile salt composition of bile.

The enterohepatic circulation of bile salts was modified since, after bile acid administration, there

TABLE 3. Oleic acid solubilization in bile salt solutions^a

Bile Salts	pH	
	6.2	6.7
	<i>Concentration (mM)</i>	
Taurochenodeoxycholate	9.23 (48%) ^b	15.00 (60%)
Taurocholate	5.15 (34%)	12.20 (55%)
Tauroursodeoxycholate	0.36 (3.5%)	7.86 (44%)

^a Oleic acid concentrations were determined at pH 6.2 and 6.7 in 10 mM bile salt solutions, at 37°C.

^b Values in parentheses indicate the % molar of solubilized oleic acid.

TABLE 4. Cholesterol micellar solubilization in bile salt oleate mixtures

Bile Salt	Oleate		
	3.9 mM	6.2 mM	9.3 mM
	<i>Cholesterol, mM</i>		
Taurochenodeoxycholate	0.72	1.03	1.10
Taurocholate	0.48	0.58	0.49
Tauroursodeoxycholate	0.26	0.09	0

Equilibrium cholesterol solubilities were determined for the three bile salts at 37°C at pH = 6.7 for three oleate concentrations: A, 3.9 mM; B, 6.2 mM; C, 9.3 mM. Bile salt concentration was kept constant (10 mM).

was an increase of the bile acid pool as shown from the biliary bile acid secretion studies. However, the three bile acids seem to induce very similar modifications of the bile acid enterohepatic circulation (see Table 2). The situation is different in man where intestinal absorption is possibly greater for dihydroxy than for trihydroxycholanic acids (23). This difference may be due to the prevalent glycoconjugation in man (with preferential passive absorption of glyco-dihydroxy bile salts) instead of exclusive taurine conjugation in mice.

Therefore, an increase of the bile acid pool during bile acid administration may explain why cholic acid feeding increases cholesterol absorption compared to controls. It cannot explain why cholic, chenodeoxycholic, and ursodeoxycholic acids do not have the same influence on cholesterol absorption. The second part of the study was therefore designed to check the influence on cholesterol solubilization of the qualitative changes in biliary bile acid composition induced by the diet.

Cholesterol solubilization

Solubilization studies were done with tauro-conjugated bile salts since in mice tauro-conjugates represent more than 80% of total bile salts. They were done with a constant bile salt concentration (10 mM) which, presumably, represented the physiological jejunal concentration during digestion of a fatty meal. In the test solutions, the total lipid concentration was 0.7 to 0.8 g/dl. Cholesterol solubility was measured without monoolein since the test meal used in acute experiments contained pure oleate and no triglyceride. Presumably intestinal pH varies during digestion. The major part of the study was done at pH 6.7 but the influence of decreasing pH was checked both for oleate and cholesterol solubilization studies.

In all the situations studied, the results generally confirm previous studies on the detergent properties

of bile acids in the presence of lecithin (9, 11, 24) or more concentrated bile salt-oleate solutions (10). The low solubilizing capacities of tauroursodeoxycholate are apparent both for oleic acid and for cholesterol. In our conditions, however, the differential effects of taurocholate and taurochenodeoxycholate are much greater. First, oleic acid solubilization is greater in the presence of taurochenodeoxycholate. On the other hand, taurocholate solubilizes more lecithin than taurochenodeoxycholate (24) and both bile salts solubilize oleate to the same extent in concentrated solutions (4% solids). The fact that a difference appears between taurocholate and taurochenodeoxycholate in diluted solutions agrees well with data concerning monoolein solubility in the presence of these two bile salts (25). This would be consistent with a very low intermicellar bile salt concentration (IMC) for taurochenodeoxycholate and a higher one for taurocholate (26). Second, cholesterol solubility in 0.8 g/dl solutions is also greatly decreased compared to that of 4 g/dl solutions. The maximal cholesterol solubility is almost twice as high in the presence of taurochenodeoxycholate than in the presence of taurocholate.

The different powers of taurocholate and taurochenodeoxycholate for cholesterol solubilization at high oleic acid/bile salt ratios may have a physiological importance since, during a fatty meal, bile salt micelles seem to contain large amounts of fatty acids (27). On the other hand, the differential effects of the bile salts do not depend on pH, and are even more marked at acidic pH. Therefore the inhibition of cholesterol absorption by ursodeoxycholic acid-supplemented diets may be explained by the poor detergent properties of the tauro-conjugate of this bile salt. On the other hand, our results cannot explain why taurocholate and taurochenodeoxycholate have opposite effects on cholesterol absorption.

Two possible ways to reconcile simply the *in vivo* results and solubilization studies can be suggested. It has been established that absorption rate depends not only on the mass of cholesterol solubilized but also on the degree of cholesterol saturation of the micelle (28). For a low cholesterol intake, taurocholate micelles are more saturated with cholesterol than taurochenodeoxycholate micelles and may deliver their cholesterol to enterocytes more easily. However this does not explain why the difference between taurocholate and taurochenodeoxycholate for absorption is the same in several studies, whatever the dose of cholesterol administered (5). Second, free bile acids contained in the diet possibly compete with cholesterol for incorporation in mixed micelles, particularly chenodeoxycholic acid which has a higher pK_a than cholic acid (29). However this phenomenon cannot explain the experimental results: the test meal which

does not contain bile acids was administered to fasted mice, so an interference between the test meal and the last ingestion of the bile acid-containing diet is excluded.

Biliary cholesterol secretion

This study confirms the importance of the total input of cholesterol in regulating biliary cholesterol secretion in mice. It appears that in this model the solubilizing capacities of the mixed micelles: bile salt–lecithin–cholesterol, are not a major determinant of biliary cholesterol secretion. In spite of their very different detergent properties, chenodeoxycholic acid and ursodeoxycholic acid have the same effects on biliary cholesterol. On the other hand, the increase of cholesterol absorption observed with cholic acid is followed by a large increase of biliary cholesterol secretion which may be associated with cholesterol gallstones (30). The difference between the effects of cholic and chenodeoxycholic acids on biliary cholesterol in this species may be explained almost entirely by their distinct effects on cholesterol absorption. This suggests that in mice the input of cholesterol regulates biliary cholesterol secretion. The results obtained with ursodeoxycholic acid show, however, that a decrease of cholesterol absorption does not reduce the biliary secretion of cholesterol. This may be consistent with our former results (31) if, as in rats (6), ursodeoxycholic acid stimulates cholesterol synthesis, thus compensating for the lack of cholesterol absorption. It must be emphasized that the possible relation between cholesterol input and biliary cholesterol is strictly species-dependent and is not observed in man (32) or in other animals (33).

In summary, we have shown that, in mice, cholesterol absorption is increased by cholic acid, unchanged by chenodeoxycholic acid, and decreased by ursodeoxycholic acid. The increase of cholesterol absorption is followed by an increase of biliary cholesterol secretion. The study of cholesterol solubilization in taurine-conjugated bile salt–oleic acid–cholesterol systems shows large differences between the three bile salts. It appears that the low detergent properties of ursodeoxycholate explain, at least in part, the low absorption observed with ursodeoxycholic acid. This suggests that the low cholesterol absorption induced by ursodeoxycholic acid feeding may well not be species-dependent. On the other hand, physicochemical properties cannot simply explain the difference between chenodeoxycholic acid and cholic acid effects. As suggested earlier, intramucosal events probably play the major role in this particular case. ■

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