Chenodeoxycholic acid normalizes elevated lipoprotein secretion and catabolism in cerebrotendinous xanthomatosis

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Abstract Cerebrotendinous xanthomatosis (CTX) is a rare inherited lipid storage disease caused by a defect in bile acid synthesis in which cholesterol and its product cholestanol are deposited in neurological and vascular tissue. Therapy with chenodeoxycholic acid but not with the 7β-epimeric ursodeoxycholic acid is usually successful. In an untreated patient, total and low density lipoprotein (LDL) cholesterol were found to be low (134 ± 11 and 78 ± 8 mg/dl, respectively). The production rate (PR) and fractional catabolic rate (FCR) of very low density (VLDL) apolipoprotein B (apoB) were, however, both markedly increased (34.7 mg/kg per day and 13.7 pools/day, respectively vs. 15.1 ± 5.0 mg/kg per day and 6.2 ± 3.8 pools/day in controls) while the PR and FCR of LDL apoB were moderately elevated (16.3 mg/kg per day and 0.65 pools/day, respectively vs. 12.9 ± 1.2 mg/kg per day and 0.52 ± 0.10 pools/day in controls). After 1 month of 750 mg/day of chenodeoxycholic acid, the FCR and PR of both VLDL and LDL apoB became normal while total plasma cholesterol increased significantly to 145 ± 18 mg/dl. In a second patient who had been receiving 750 mg/day of chenodeoxycholic acid for 6 months lipoprotein kinetics were normal. These parameters did not change when the subject was switched to 750 mg/day ursodeoxycholic acid. We postulate that cholesterol biosynthesis in CTX is derepressed by a diminished hepatic pool of chenodeoxycholic acid and that the elevated secretion of apoB is a response to the increased rate of cholesterol production. —**Tint, G. S., H. Ginsberg, G. Salen, N-A. Le, and S. Shefer.** Chenodeoxycholic acid normalizes elevated lipoprotein secretion and catabolism in cerebrotendinous xanthomatosis. *J. Lipid Res.* 1989. **30:** 633–640.

Supplementary key words VLDL • LDL • apoB • lipoprotein kinetics • ursodeoxycholic acid

Cerebrotendinous xanthomatosis (CTX) is a rare inherited lipid storage disease characterized by defective hydroxylation of the cholesterol side chain during bile acid biosynthesis (1, 2). As a consequence, the production rate of cholesterol and its 5α-saturated derivative, cholestanol, is markedly increased (3), bile acid production is reduced (4, 5), and increased amounts of polyhydroxylated sterols (bile alcohols), which cannot be transformed to bile acids, are made and excreted into bile and urine (5–8). Clinically, patients suffer from premature atherosclerosis, tendon xanthomas, cerebellar ataxia, and dementia due to the deposition of large quantities of cholesterol and cholestanol in the major blood vessels, tendons, and brain. The development of these symptoms is surprising since plasma cholesterol concentrations are usually at or below normal (1–3, 9, 10).

Most patients can be treated successfully with 750 mg/day of chenodeoxycholic acid (CDCA). This naturally occurring bile acid suppresses cholesterol, cholestanol, bile alcohol, and bile acid synthesis (1, 7, 8, 11, 12). Plasma cholesterol usually increases slightly but cerebrospinal fluid cholesterol and plasma and cerebrospinal fluid cholestanol concentrations decline (1, 11–13). Clinical symptoms are either ameliorated or do not progress. In contrast, treatment with ursodeoxycholic acid (UDCA), the 7β-hydroxy epimer of CDCA, is completely ineffective (12, 14).

As there is considerable sterol deposition in the face of low total cholesterol and low density lipoprotein (LDL) plasma concentrations (1, 2, 9, 10) one might expect to find other defects of lipoprotein metabolism as well. Indeed, we found that high density lipoprotein (HDL) cho-

Abbreviations: CTX, cerebrotendinous xanthomatosis; HMG-CoA reductase, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; FCR, fractional catabolic rate; PR, production rate; VLDL, very low density lipoprotein; LDL, low density lipoprotein; apoB, apolipoprotein B; CDCA, chenodeoxycholic acid, 3α,7α-dihydroxy-5β-cholanic acid; UDCA, ursodeoxycholic acid, 3α,7β-dihydroxy-5β-cholanic acid; cholic acid, 3α,7α,12α-trihydroxy-5β-cholanic acid; cholestanol, 5α-cholestan-3β-ol.

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lesterol was significantly reduced from normal levels and that the ratio of cholesterol to apoprotein in HDL was abnormally low (10). Recently, Ballantyne et al. (15) reported that both the fractional catabolic rate (FCR) and the production rate (PR) of LDL apolipoprotein B (apoB) were significantly elevated in a patient with CTX and that both parameters returned to normal during treatment with CDCA.

Studies using autologous radiolabeled lipoprotein tracers have suggested that, in most cases, the majority of LDL apoB is derived from the catabolism of very low density lipoprotein (VLDL) apoB (16, 17). Thus, the normalization of LDL kinetics in CTX patients in response to CDCA therapy may result from reduced entry of VLDL apoB into the plasma (15). Evidence for this possibility arises from studies demonstrating that CDCA suppresses both the fractional catabolic rate and the synthesis of VLDL triglycerides in hyperlipidemic patients (18). UDCA, in contrast, does not change plasma total, LDL, VLDL, or HDL cholesterol concentrations or VLDL triglyceride kinetics (19) and is, thus, unlikely to affect apoB metabolism.

To explore the mechanisms whereby these two bile acids might alter cholesterol and apoB metabolism, we have determined the effect of both CDCA and UDCA on VLDL and LDL apoB kinetics in two CTX patients.

METHODS

Clinical

Subject J. C. was a 42-year-old black man weighing 59 kg and W. H. was an 80 kg, 53-year-old white male. Complete clinical and biochemical information have been published elsewhere (2–5, 10–13). During the study they were housed at the Veterans Administration Medical Center, East Orange, NJ. Patient J. C. had not been treated for CTX for the 4 months preceding the study. Patient W. H. had been receiving 750 mg/day CDCA for 6 months. The bile acid was stopped 2 days before the current study began. All experimental protocols were approved by the Human Studies Committees of the VA Medical Center and the University of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, NJ.

Measurement of cholestanol

Plasma cholestanol was measured by the method of Ishikawa et al. (20). One ml of plasma was hydrolyzed in 1 N ethanolic NaOH. The neutral sterols were extracted with hexane and were quantitated on a gas–liquid chromatography column packed with 1% SP-1000 (Applied Science Laboratories, State College, PA) using 5α-cholestane as an internal standard (12).

Experimental protocol

Baseline measurements of plasma total and lipoprotein cholesterol and triglycerides and VLDL and LDL apoB kinetics were carried out in the untreated subject J. C. and in the CDCA-treated subject W. H. J. C. was then given 750 mg/day CDCA and W. H. received 750 mg/day oral UDCA (Gipharmex, Milan, Italy) for 1 month and the measurements were repeated. The experimental protocol employed was that of Ginsberg, Le, and Gibson (21). Briefly, after several days of a solid food diet of 45% carbohydrate, 40% fat, and 15% protein with a polyunsaturated/saturated fat ratio of 0.4 and 150 mg cholesterol/1000 kcal per day, plasma was obtained following an overnight fast and VLDL and LDL were isolated. Four days later the subjects were given 50 μCi of ^{131}I-labeled VLDL intravenously and 18 blood samples were taken over the next 24 h (22). In addition, 300 μCi of [^{3}H]glycerol was administered to patient W. H. During this time the subjects consumed a liquid formula that consisted of 75% carbohydrate and 25% protein and provided 60% of their usual daily caloric intake. Three days after the injection of the VLDL, 25 μCi of ^{125}I-labeled LDL was administered and eight blood samples were drawn over the following 24 h. The subjects returned to the solid food diet on that day and, thereafter, fasting blood samples were obtained for 12–14 days. All subjects received 100 mg of iodide as potassium iodide twice daily during the study period.

Laboratory procedures

Procedures identical to those used by Ginsberg, Le, and Gibson (21) for the measurement of VLDL and LDL apoB kinetics were employed. VLDL was isolated at plasma density (d 1.006 g/ml) by ultracentrifugation as described by Melish et al. (22). LDL was separated by three sequential steps which included ultracentrifugation in a 60 Ti rotor at 59,000 rpm (d 1.025–1.060 g/ml), in a 75 Ti rotor at 65,000 rpm (d 1.025 g/ml), and in a 40.3 rotor at 39,000 rpm at d 1.063 g/ml. Each step was carried out at 10°C for 20–24 h (21, 23, 24). The lipoproteins were iodinated by the procedure of Bilheimer, Eisenberg, and Levy (24), diluted with 0.15 M NaCl and human serum albumin (final concentration of albumin 5 g/dl), filtered, and stored in sterile vials. [2-^{3}H]Glycerol (New England Nuclear, Boston, MA) was diluted to a concentration of 300 μCi/ml and filtered before use.

VLDL and LDL were isolated by sequential ultracentrifugation from the plasma samples obtained after the radiolabeled lipoproteins and [^{3}H]glycerol were injected. In the VLDL fraction, apoB was isolated as described by Le et al. (25) using 1,1',3,3'-tetramethylurea. ApoB specific activity in VLDL and LDL and VLDL triglyceride specific activity were determined as described previously (21, 22). Gamma and beta radioactivity were deter-

mined in scintillation counters (Packard Instruments, Downers Grove, IL). Protein was measured by the method of Lowry et al. (26).

Total plasma and ultracentrifugally isolated VLDL and LDL cholesterol and triglyceride concentrations were measured by enzymatic procedures in an ABA-100 autoanalyzer (Abbot Laboratories, Chicago, IL). HDL cholesterol was determined according to a modified Lipid Research Clinics methodology (27) while apoB in VLDL and LDL were determined by radioimmunoassay (21).

Data analysis

We used the model described by Melish et al. (22) to analyze the VLDL apoB specific activity data. This is a two-compartment model in which the labeled VLDL apoB in the rapidly turning over plasma pool is either converted to a slowly catabolized plasma pool, is transformed to IDL and/or to LDL, or is removed directly from the plasma as VLDL. It is further assumed that the slowly catabolized VLDL apoB is removed directly from plasma without conversion to more dense lipoproteins and that the ^{131}I-labeled VLDL-apoB is injected into both compartments. The LDL apoB was analyzed by the model developed by Langer, Strober, and Levy (23) which consists of an intravascular and an extravascular compartment. The LDL apoB fractional catabolic rate (FCR) and production rate were calculated for the intravascular pool. Plasma VLDL triglyceride kinetics were analyzed as previously described (21) using a model that includes fast and slow secretory pools in the liver and two pools in the plasma compartment. All of the curve fitting was carried out by a nonlinear regression program which estimates transfer rates directly from the experimental data (28).

RESULTS

In **Table 1** we have listed the plasma total cholesterol, cholestanol, and triglyceride concentrations for the two CTX patients and for control subjects. In **Table 2** are the corresponding measurements for plasma VLDL, LDL and HDL cholesterol and VLDL triglycerides. Before treatment in patient J. C. the plasma total cholesterol and triglyceride concentrations (Table 1) and VLDL and LDL cholesterol (Table 2) were markedly reduced compared to controls. But, plasma cholestanol was elevated to more than three times normal (Table 1). Treatment of J. C. with 750 mg/day CDCA for 1 month caused a slight but statistically significant ($P < 0.05$) elevation of plasma total cholesterol, a 50% reduction in plasma cholestanol (Table 1), and a lowering of VLDL triglycerides (Table 2).

In subject W. H. the baseline study was carried out during CDCA therapy. At this time plasma total (Table 1) and VLDL and LDL cholesterol (Table 2) were significantly below normal while the concentration of HDL cholesterol was only about one-half of the level seen in age-matched controls (Table 2). In response to CDCA, the concentration of cholestanol in W. H. had been reduced from its untreated value of 2–3 mg/dl (10, 12) to a high normal concentration of 0.7 mg/dl (Table 1). Plasma triglycerides were within the normal range of those reported in the Lipid Clinics Prevalence study (27) but were significantly elevated compared to our younger normolipidemic controls (29) (Table 1). When W. H. was switched from CDCA 750 mg/day to UDCA 750 mg/day his plasma total cholesterol declined (Table 1) while plasma LDL and VLDL cholesterol increased (Table 2). The most striking effect was, as we have reported previ-

TABLE 1. Plasma total cholesterol, cholestanol, and triglycerides (mean ± SD)

Subject	Plasma Cholesterol	Plasma Cholestanol	Plasma Triglycerides
		mg/dl (n)	
J. C. (CTX)			
Untreated	134 ± 11 (18)[a]	2.1	64 ± 14 (18)[b]
CDCA	145 ± 18 (18)[a]	1.3	67 ± 11 (18)[b]
Significance[c]	$P < 0.05$		NS
W. H. (CTX)			
CDCA	148 ± 11 (18)[a]	0.7	177 ± 13 (18)[d]
UDCA	139 ± 11 (18)[a]	4.5	167 ± 8 (18)
Significance[e]	$P < 0.05$		NS
Controls			
For J. C.	207 ± 37 (384)[f]	0.6 ± 0.02 (10)[g]	126 ± 90 (167)[f]
For W. H.	213 ± 37 (340)[f]	0.6 ± 0.02 (10)[g]	153 ± 101 (340)[f]

[a] $P < 0.0001$ with respect to control subjects.
[b] $P < 0.005$ with respect to control subjects.
[c] Untreated versus CDCA.
[d] $P < 0.02$ with respect to control subjects.
[e] CDCA versus UDCA.
[f] Age-matched males, Lipid Research Clinics Prevalence Study (30).
[g] Normolipidemic controls from Shore et al. (10).

TABLE 2. Lipoprotein cholesterol and triglycerides (mean ± SD)

	Cholesterol			VLDL Triglyceride
	VLDL	LDL	HDL	
	mg/dl (n)			
J. C. (CTX)				
Untreated	7.3 ± 2.5 (18)[a]	78 ± 8 (14)[b]	45 ± 2 (5)	35 ± 12 (18)
CDCA	5.0 ± 1.0 (18)[a]	83 ± 8 (14)[b]	48 ± 6 (5)	25 ± 6 (18)[c]
Significance[d]	NS	NS	NS	$P < 0.05$
W. H. (CTX)				
CDCA	15 ± 2 (18)[c]	72 ± 7 (14)[b]	28 ± 5 (5)[a]	100 ± 9 (18)[b]
UDCA	20 ± 4 (18)	91 ± 5 (14)[b]	25 ± 2 (5)[a]	118 ± 11 (18)[b]
Significance[e]	$P < 0.0001$	$P < 0.0001$	NS	NS
Controls[f]				
For J. C. (n = 384)	26 ± 24	136 ± 31	44 ± 12	41 ± 8 (5)[g]
For W. H. (n = 340)	27 ± 20	142 ± 31	44 ± 1	141 ± 8 (5)[g]

[a] $P < 0.005$ with respect to control subjects.
[b] $P < 0.0001$ with respect to control subjects.
[c] $P < 0.02$ with respect to control subjects.
[d] Untreated versus CDCA.
[e] CDCA versus UDCA.
[f] Age-matched males, Lipid Research Clinics Prevalence Study (30).
[g] Normolipidemic controls from Ginsberg et al. (29).

ously (12), a sixfold increase in his plasma cholestanol (Table 1).

VLDL apoB and triglyceride concentrations and kinetic parameters are shown in **Table 3.** The corresponding values for LDL apoB are listed in **Table 4.**

In J. C. prior to treatment, the level of VLDL apoB was no different than in our normolipidemic subjects, but both the VLDL apoB fractional catabolic rate (FCR) and VLDL apoB production rate (PR) were at least two standard deviations above the rates seen in our controls (Table 3). CDCA reduced the VLDL apoB FCR to one-third and the apoB PR to one-half of their pretreatment values. A plot of the VLDL apoB specific activity versus time before and during CDCA is shown in **Fig. 1.** Associated with these reductions was a 20% increase in VLDL apoB. As previously reported (15), both the synthesis and the FCR of LDL apoB before treatment were moderately elevated (Table 4). The time course of the LDL apoB specific activity is depicted in **Fig. 2.** Apparently, the increased input of apoB into LDL was offset by its increased catabolism because the LDL apoB concentration remained within the normal range. Treatment

TABLE 3. Very low density lipoprotein apolipoprotein B and triglyceride kinetic parameters (mean ± SD)

	VLDL apolipoprotein B			VLDL Triglyceride	
	Concentration	Fractional Catabolic Rate	Production Rate	Fractional Catabolic Rate	Production Rate
	mg/dl (n)	*pools/day*	*mg/kg/day*	*pools/hr*	*mg/kg/hr*
J. C. (CTX)					
Untreated	5.6 ± 0.3 (5)	13.7	34.7		
CDCA	6.6 ± 0.3 (5)	4.8	14.2		
Significance[a]	$P < 0.001$				
W. H. (CTX)					
CDCA	6.6 ± 0.8 (5)	4.8	14.3	0.25	14.0
UDCA	7.4 ± 1.0 (5)	4.6	15.2	0.30	19.3
Significance[b]	NS				
Controls	5.8 ± 1.4[c]	6.2 ± 3.8[c]	15.1 ± 5.0[c]	0.21 ± 0.02[d]	10.6 ± 0.95[d]

[a] Untreated versus CDCA treatment.
[b] CDCA versus UDCA treatment.
[c] Normolipidemic controls (n = 5) from Ginsberg et al. (29).
[d] Normolipidemic controls (n = 13) from Howard et al. (55).

TABLE 4. Low density lipoprotein apolipoprotein B kinetic parameters (mean ± SD)

	Concentration	Fractional Catabolic Rate	Production Rate
	mg/dl (n)	*pools/day*	*mg/kg/day*
J. C. (CTX)			
Untreated	56 ± 5 (5)	0.65	16.3
CDCA	46 ± 5 (5)	0.48	9.9
Significance[a]	NS		
W. H. (CTX)			
CDCA	58 ± 2 (5)	0.44	11.0
UDCA	69 ± 4 (5)	0.38	11.8
Significance[b]	$P < 0.001$		
Controls[c]	51 ± 11	0.52 ± 0.10	12.9 ± 1.2

[a]Untreated versus CDCA treatment.
[b]CDCA versus UDCA treatment.
[c]Normolipidemic controls (n = 5) from Ginsberg et al. (29).

with CDCA reduced both the LDL apoB FCR and PR by 30–40%.

Neither the VLDL (Table 3) and LDL apoB (Table 4) concentrations nor their corresponding kinetic parameters were abnormal in subject W. H. during CDCA therapy. After 1 month of treatment with UDCA no significant changes in any of these were detected (Table 4 and **Fig. 3**). It is noteworthy, however, that even during treatment with CDCA the synthesis of VLDL triglyceride was elevated and this value increased noticeably when UDCA was substituted for CDCA (Table 3). Nevertheless, plasma total (Table 1) and VLDL triglycerides (Table 2) did not change appreciably.

DISCUSSION

The present study demonstrates a number of sterol and lipoprotein abnormalities associated with the rare lipid storage disease CTX. As we have reported previously (1, 3, 10–12) plasma total, LDL, and HDL cholesterol are often abnormally reduced while plasma cholestanol is markedly elevated (Tables 1 and 2). In addition, we found that in untreated CTX both VLDL apoB entry and fractional removal from plasma were greatly elevated (Table 3, Fig. 1). We have also confirmed the recent observation (15) that in CTX the production and fractional catabolism of LDL apoB are moderately elevated as well and that both kinetic parameters can be reduced by CDCA (Table 4, Fig. 2). The pool of CDCA is markedly depressed in CTX (1–5) and treating subject J. C. with 750 mg/day CDCA for 1 month normalized both the production and catabolism of VLDL apoB and LDL apoB. The efficacy of CDCA in suppressing elevated apoB kinetics is also supported by the finding that the kinetics of VLDL apoB and LDL apoB were normal in patient W. H. who had been treated with 750 mg/day CDCA for 6 months (Tables 3 and 4, Fig. 3).

As Ballantyne et al. (15) postulated, the increased secretion of LDL apoB in CTX seems to be driven by a greatly elevated input of VLDL apoB into the plasma (Table 3) although the surprisingly large magnitude of the VLDL flux could not have been deduced from the LDL apoB kinetic data alone. Nevertheless, the highly efficient removal of VLDL and LDL apoB (Tables 3 and 4) must be more than sufficient to accommodate the increased apoB production as both LDL apoB and plasma total and LDL cholesterol in untreated CTX are found to be reduced (1, 3, 10, 12, 15). CDCA treatment, which reduced the VLDL and LDL apoB production rates, was also associated with impressive reductions in the FCR of apoB in both lipoproteins (Tables 3 and 4).

The synthesis of bile acids is reduced in CTX (3–5) due to a defective enzyme in the bile acid biosynthetic pathway (1, 2, 5, 31, 32). Because of this, a considerable quantity of cholesterol is converted (2–5, 7, 8) to polyhydroxylated bile acid intermediates (bile alcohols). It has been hypothesized (15) that the shunting of cholesterol into the production of bile acids and bile alcohols might be large enough to reduce the concentration of cholesterol in a key regulatory pool in the hepatocytes. This would induce the liver to increase its synthesis of cholesterol and to activate or synthesize additional apoB/E receptors. While this is an attractive model that expresses how cultured fibroblasts respond when their supply of exogenous cholesterol is reduced (33, 34), it probably does not describe accurately the situation in the CTX liver as the catabolism of cholesterol by conversion to bile acids and bile alcohols in CTX may only be moderately elevated. Fecal and urinary bile alcohol excretion (4, 7, 8) plus bile acid synthesis (3–5) totals 350 to 650 mg/day which is within the observed normal range for total bile acid synthesis (5, 18, 35). Although W. H., when untreated, can make as much as 850 mg/day of bile acids and bile alcohols (G. S. Tint,

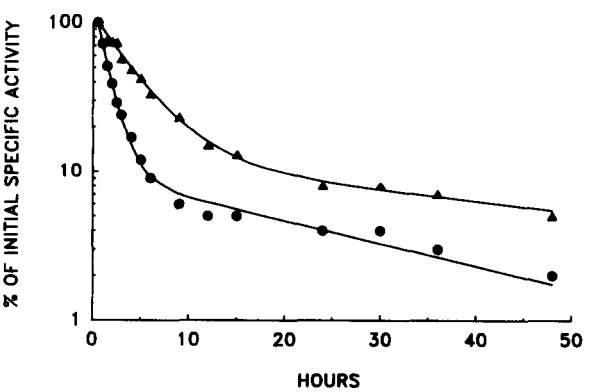

Fig. 1. CTX patient J. C. Percent of initial plasma VLDL apoB specific activity versus time after pulse labeling; (●) untreated; (▲) CDCA 750 mg/day.

unpublished observations) the diversion of cholesterol to the bile acid biosynthetic pathway is far less than the 4.1-fold increase in bile acid production seen in controls given bile acid sequestrants (36). Another argument against the above hypothesis is our observation that the concentrations of cholesterol in the liver of patient J. C. (37) and in another CTX subject (9) were not appreciably different from concentrations measured in control subjects (38–41). Nevertheless, it is still possible that cholesterol in a small key regulatory microsomal pool might be greatly diminished in CTX.

An alternative hypothesis to the above arises from suggestions (42, 43) that, in the liver, bile acids in addition to cholesterol can also affect cholesterol biosynthesis. Measurements in patients with cholesterol gallstones support this possibility. In these individuals the activity of the rate-controlling enzyme for cholesterol synthesis, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase (37, 38–41, 44, 45) is elevated in the face of increased liver total and microsomal cholesterol levels (37, 39, 40, 44). The defect in this disease seems to be that bile acid biosynthesis is relatively low (31, 35, 38, 45–47). When the bile acid pool is expanded by oral CDCA the activity of HMG-CoA reductase is markedly suppressed (39, 40, 44, 45), plasma total and LDL cholesterol increase (48), but hepatic cholesterol levels are either maintained (38) or reduced further (39, 44). Thus, at least in cholesterol gallstone disease, the level of microsomal cholesterol does not appear to have the controlling influence on cholesterol synthesis as it does in cultured fibroblast, and bile acid concentrations are of considerable importance.

Concomitant with increased cholesterol synthesis in untreated CTX, apoB-containing lipoproteins are secreted into plasma at an unusually rapid rate. But, when hepatic cholesterol production is suppressed with CDCA, apoB production is also reduced (Tables 3 and 4 and reference 15). Ginsberg et al. (49) and Arad, Ramakrishnan, and Ginsberg (50) have recently postulated that

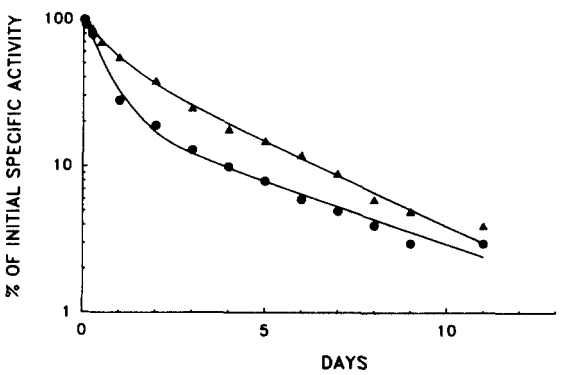

Fig. 2. CTX patient J. C. Percent of initial plasma LDL apoB specific activity versus time after pulse labeling; (●) untreated; (▲) CDCA 750 mg/day.

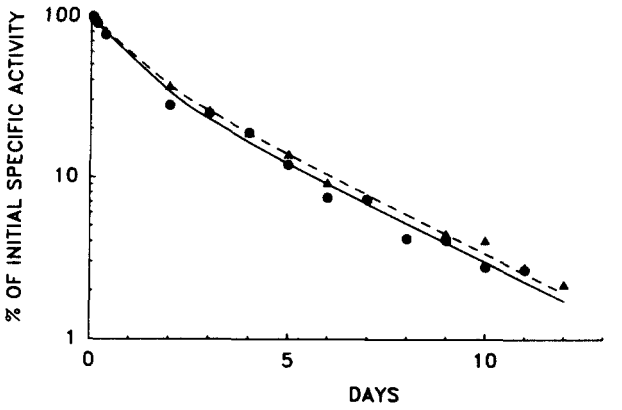

Fig. 3. CTX patient W. H. Percent of initial plasma LDL apoB specific activity versus time after pulse labeling; (●) baseline CDCA 750 mg/day; (▲) UDCA 750 mg/day.

the rate at which apoB is secreted into VLDL and LDL may be coupled to the rate at which cholesterol is being synthesized by the liver. If this suggestion proves to be true, it provides a mechanism which explains the elevated VLDL and LDL apoB PR in CTX.

The very rapid clearance of VLDL and LDL apoB in untreated CTX patients is most likely due to increased synthesis of hepatic apoB/E receptors (15, 33, 34, 51). Hence, our results suggest that in CTX apoB/E receptor activation or synthesis, cholesterol production, and the secretion of apoB-containing lipoproteins into the plasma are all coupled. The deficiency of CDCA in CTX may be a factor as cholic acid has been observed to suppress apoB/E receptor activity in the dog (52), UDCA appears to increase LDL uptake in hamsters (53), while it has been suggested that oral CDCA may reduce LDL clearance in humans (48).

Our finding that cholesterol and lipoprotein metabolism were little affected after patient W. H. was switched from 6 months of CDCA to UDCA should not be surprising. UDCA, when given for a month or more, seems equally capable of suppressing the activity of hepatic HMG-CoA reductase (38, 42). Replacing CDCA with UDCA probably did not greatly alter the subject's already reduced rate of hepatic cholesterol biosynthesis.

It is noteworthy that before treatment triglycerides were normal in patient J. C. while in W. H., as well as in the CTX subject studied by Ballantyne et al. (15), plasma triglyceride concentrations were elevated and remained so even during CDCA therapy. Thus, abnormal triglyceride metabolism, although not uncommon in CTX, is not universal for the disease. These results are, nevertheless, somewhat unexpected as it has been noted that treatment of hypertriglyceridemic patients with CDCA usually reduces both the plasma concentration (18, 48, 54) and the endogenous synthesis (18) of triglycerides.

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