Effects of cholestyramine and chenodeoxycholic acid on the metabolism of endogenous triglyceride in hyperlipoproteinemia

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Abstract Previous studies conducted under basal conditions have suggested a linkage between the formation of plasma triglyceride and the degradation of cholesterol to bile acids. To further examine this relationship, plasma endogenous triglyceride kinetics were determined using [^{3}H]glycerol in 26 hyperlipidemic subjects before and during stimulated (cholestyramine treatment) and inhibited (chenodeoxycholic acid treatment) bile acid synthesis. All patients with hyperlipoproteinemia (HLP) type II ($n = 9$) treated with cholestyramine (12 g daily for 2–4 months) displayed increased apparent biosynthesis (12.8 ± 1.5 vs. 9.7 ± 1.2 μmol kg^{-1}hr^{-1}, mean ± SEM, $P < 0.005$) and an elevated apparent fractional turnover rate (0.230 ± 0.017 vs. 0.176 ± 0.014 hr^{-1}, $P < 0.001$) as determined over a 10-hr period, in spite of essentially unchanged plasma triglyceride concentrations. No consistent effect of this therapy was encountered in the five patients studied with type IV HLP. Chenodeoxycholic acid feeding (1.9 mmol daily for 3–4 months) resulted in a reduced apparent synthesis of plasma triglycerides both in type IIa ($n = 5$, 7.9 ± 0.5 vs. 13.1 ± 1.2 μmol kg^{-1}hr^{-1}, $P < 0.01$) and type IV HLP ($n = 7$, 15.5 ± 1.8 vs. 23.6 ± 3.7 μmol kg^{-1}hr^{-1}, $P < 0.02$). Furthermore, a 20–25% reduction of the apparent fractional turnover rate was seen, and the plasma concentration of triglycerides was reduced by about 15%. It is concluded that the present experimental conditions that primarily influence cholesterol and bile acid biosynthesis also affect the metabolism of plasma triglycerides—and presumably that of very low density lipoprotein—in a regulatory manner. Hypothetically, this may be achieved via a hepatic pool of newly synthesized cholesterol.

Supplementary key words cholesterol · bile acids · very low density lipoprotein

Several lines of evidence indicate that changes in plasma triglyceride turnover are associated with changes in the metabolism of cholesterol. Hyperlipoproteinemia (HLP) type IV (1) is often characterized by enhanced cholesterogenesis (2). This abnormality is in general balanced by an increased elimination of cholesterol as bile acids (3). The formation of plasma triglyceride appears to correlate positively with bile acid production in patients with HLP type IIa and type IV studied under basal conditions (4). Moreover, the reduced triglyceride synthesis induced by weight reduction (5) or by administration of clofibrate (6) or nicotinic acid (7) to patients with the type IV lipoprotein pattern is accompanied by a decreased formation of bile acids (3, 8, 9).

The synthesis of bile acids is regulated by a negative feedback control (for a review, see ref. 10). Administration of cholestyramine, which interferes with bile acid absorption, is accompanied by an enhanced formation (11, 12) and an increased fecal excretion (13–16) of bile acids. In accordance with the principles of feedback inhibition, bile acid feeding results in a reduced conversion of cholesterol to bile acids (10, 17–20). Considering the apparent link between the production of plasma triglycerides and bile acids mentioned above, it appears of major interest to study plasma triglyceride metabolism under conditions that primarily may influence cholesterol and bile acid biosynthesis. As part of such a study, the present investigation was designed to examine the effect of cholestyramine and chenodeoxycholic acid (CD) treatment on the metabolism of plasma trigycerides in patients with HLP type II and type IV. A preliminary report on some of these findings has been published (21).

METHODS

Subjects

The study comprised 13 patients with type IIa, one with type IIb, and 12 with type IV HLP. Clinical diagnoses and basal data are listed in **Tables 1** and **2.** Altogether 19 of the patients had participated in a study reported in an adjacent paper (4), where a more detailed description of the conditions for acceptance

Abbreviations: C, cholic acid; CD, chenodeoxycholic acid; HLP, hyperlipoproteinemia; LDL, low density lipoprotein; VLDL, very low density lipoprotein.

TABLE 1. Data for patients before and during treatment with cholestyramine

Patient, Type of Hyperlipoproteinemia	Sex Age	Body Weight			Previous History, Present Symptoms[b]
		Before	During	Before Relative[a]	
	yr	*kg*			
1. EA IIa	F 63	73	71	120	IHD
2. GB IIa	F 56	52	53	87	
3. IE IIa	F 24	60	60	95	
4. EHn IIa	F 41	46	46	92	
5. LP IIb	F 54	68	68	111	
6. AW IIa	F 58	46	46	77	IHD, GBD
7. KH IIa	M 49	65	63	93	
8. BJ IIa	M 34	83	83	117	IHD
9. BLg IIa	M 33	70	71	93	
Mean	46	63	62	98	
± SEM	± 4	± 4	± 4	± 5	
10. MJ IV	F 69	60	60	98	HT, GBD
11. SGn IV	M 51	91	91	108	IHD, GBD
12. SO IV	M 69	86	84	110	HT, GBD
13. LO IV	M 58	83	83	106	IHD, GBD
14. NH IV	M 53	77	77	100	IHD, HT, DM
Mean	60	79	79	104	
± SEM	± 3	± 5	± 5	± 2	

[a] Calculated as $\frac{\text{weight (kg)}}{\text{height (cm)} - 100} \times 100\%$.

[b] IHD, ischemic heart disease; HT, hypertension; GBD, gallbladder disease; DM, diabetes mellitus.

into the study will be found. Some of the subjects were being treated continuously with digitalis, diuretics, and /or nitrate preparations. This therapy was kept unchanged during the present investigations and in the interval between them. During the preceding months, none of the patients had been treated with drugs or diets known to interfere with lipoprotein metabolism.

TABLE 2. Data for patients before and during treatment with CD

Patient, Type of Hyperlipoproteinemia	Sex Age	Body Weight			Previous History, Present Symptoms[b]
		Before	During	Before Relative[a]	
	yr	*kg*			
1. MM IIa	F 48	63	62	95	GBD
2. EK IIa	M 42	80	82	101	
3. ES IIa	M 48	68	69	88	
4. KJ IIa	M 57	73	72	99	
5. KL IIa	M 65	82	84	110	
Mean	52	73	74	99	
± SEM	± 4	± 4	± 4	± 4	
6. EC IV	F 65	60	60	97	HT, GBD
7. AL IV	M 40	76	75	89	
8. PK IV	M 50	76	76	109	
9. RC IV	M 54	77	77	110	GBD
10. TL IV	M 55	84	85	111	
11. TÅ IV	M 57	101	100	120	HT
12. HH IV	M 66	87	84	109	IHD, GBD
Mean	55	80	80	106	
± SEM	± 3	± 5	± 5	± 4	

[a] Calculated as $\frac{\text{weight (kg)}}{\text{height (cm)} - 100} \times 100\%$.

[b] IHD, ischemic heart disease; HT, hypertension; GBD, gallbladder disease.

Experimental procedure

The patients were hospitalized during the studies and maintained on a standardized diet of natural type (cf. 1, 4). The energy intake was adjusted to keep the body weight constant. After at least one week, when the plasma lipids had stabilized at a constant level, the patients received an intravenous injection of [^{3}H]glycerol (40 μCi) in the morning after an overnight fast. Venous blood samples were obtained at 30-min intervals from 2 to 6 hr and then at 7, 8, and 10 hr after administration of the isotope. Plasma radioactivity was determined in all samples, and the concentration of plasma triglycerides was determined in the samples collected at 0,2,4,6, and 8 hr.

Following the first study, 14 patients (eight with type IIa, one with type IIb, and five with type IV HLP) were treated with cholestyramine (Questran, Bristol, Sweden), 4 g three times a day for 2–4 months. Cholestyramine was administered as a powder. The other patients (five with type IIa and seven with type IV HLP) were prescribed chenodeoxycholic acid (CD) (Chendol, Draco, Sweden), 0.95 mmol twice a day for 3–4 months, given in 0.32-mmol capsules. Both drugs were tolerated without obvious discomfort, and routine indices of hepatic function (serum bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) were unchanged and within normal limits in all patients. At the end of the treatment period, the patients were hospitalized once again, and the plasma triglyceride kinetics were reexamined during medication as described above.

Material

[2-^{3}H]Glycerol (sp act 200 μCi/μmol) was obtained from the Radiochemical Centre, Amersham, England. Prior to use, the isotope was purified by evaporation to dryness in vacuo to eliminate [^{3}H]water. The residue was dissolved in 70% ethanol and diluted with saline before injection.

Methods

Cholesterol and triglycerides were determined with a Technicon AutoAnalyzer (Technicon Instruments Corp., Tarrytown, NY). Lipoprotein phenotyping (1) was performed as described earlier (3, 4).

Plasma triglyceride kinetics were determined by the method of Farquhar et al. (22) as described by Nikkilä and Kekki (6, 23, 24). Details of the experimental

procedure have been given in the preceeding paper (4). In no case did the plasma triglyceride concentration show variations of more than ±5% of the initial value. The radioactivity (dpm/ml) was plotted against time on a semilogarithmic scale and the curve was analyzed with a digital computer. One patient was excluded from the study, because his triglyceride elimination curve was found to be composed of more than one exponential slope.

The apparent fractional turnover rate of endogenous plasma triglyceride (k, hr^{-1}) was determined from the exponential descending slope of the plasma radioactivity curve. Before treatment with cholestyramine, the standard error of the individual fractional turnover rate determinations averaged 0.011 (7%) and during medication averaged 0.009 (5%). The correlation coefficients ranged from 0.917 to 0.995 before and from 0.929 to 0.991 after institution of this treatment ($P < 0.001$ in all cases). In the patients given CD, the standard error of individual fractional turnover rate determinations averaged 0.010 (7%) before and 0.010 (7%) during medication. Correlation coefficients ranging from 0.934 to 0.993 before and from 0.924 to 0.987 during treatment were observed ($P < 0.001$ in all cases). Thus in all patients, except the one excluded as mentioned above, single-exponential decay curves were obtained.

The apparent plasma triglyceride production rate, expressed in $\mu mol\ kg^{-1}hr^{-1}$, was calculated from the apparent fractional turnover rate and the mean plasma triglyceride concentration during the experiment after correction for overweight as described in the preceding paper (4). The standard error in the calculation of triglyceride synthesis in the individual subjects, considering both the error in fractional turnover rate and triglyceride variability, averaged 8% before and 6% during medication with cholestyramine, and 8% before and 9% during CD treatment.

In this calculation of "apparent" triglyceride synthesis the possible emergence of a slow exponential component of the curve after 10 hr is ignored, as discussed in the preceding paper (4). This potential limitation must be kept in mind when interpreting the results (cf. Discussion).

Statistical analysis

Data are presented as means ± SEM. The significance of differences was evaluated by Student's paired t test (25).

TABLE 3. Effect of cholestyramine on plasma lipid levels and triglyceride kinetics in patients with hyperlipoproteinemia

Patient, Type of Hyperlipoproteinemia	Plasma Cholesterol[a]		Plasma Triglyceride[a]					
			Concentration		Apparent Fractional Turnover Rate		Apparent Turnover Rate	
	Before	During	Before	During	Before	During	Before	During
	mmol/l		*mmol/l*		*hr^{-1}*		*$\mu mol/kg/hr$*	
1. IIa	9.1	6.5	1.3	1.5	0.165	0.238	8.4	14.4
2. IIa	8.7	7.3	0.7	0.7	0.215	0.269	6.8	8.5
3. IIa	8.4	6.9	0.8	1.2	0.147	0.169	5.3	9.1
4. IIa	8.6	8.0	1.9	1.2	0.113	0.197	9.7	10.6
5. IIb	7.9	6.2	2.3	2.6	0.168	0.207	16.0	22.4
6. IIa	6.3	4.6	1.2	1.1	0.234	0.289	12.7	14.3
7. IIa	9.1	6.7	1.3	1.1	0.187	0.229	10.9	11.3
8. IIa	7.8	5.0	1.3	1.3	0.225	0.307	11.7	15.9
9. IIa	7.8	5.1	1.0	1.1	0.131	0.167	5.9	8.3
Mean	8.2	6.3	1.3	1.3	0.176	0.230	9.7	12.8
± SEM	± 0.3	± 0.4[c]	± 0.2	± 0.2	± 0.014	± 0.017[b]	± 1.2	± 1.3[b]
10. IV	5.1	5.0	4.6	5.1	0.112	0.114	23.3	26.1
11. IV	7.6	6.8	3.0	2.6	0.170	0.130	21.6	14.3
12. IV	6.4	5.6	5.1	4.9	0.094	0.081	20.1	16.9
13. IV	7.1	8.1	3.1	3.7	0.211	0.202	28.1	32.1
14. IV	7.7	7.8	3.1	3.5	0.157	0.107	21.9	16.9
Mean	6.8	6.7	3.8	4.0	0.149	0.127	23.0	21.3
± SEM	± 0.5	± 0.6	± 0.4	± 0.4	± 0.021	± 0.020	± 1.4	± 3.4

[a] To convert mmol/l to mg/dl multiply cholesterol concentrations by 38.7 and triglyceride concentrations by 0.1 × mol wt of triglyceride (e.g., 88.5 for triolein).
[b] Significantly different from pretreatment value, $P < 0.005$.
[c] Significantly different from pretreatment value, $P < 0.001$.

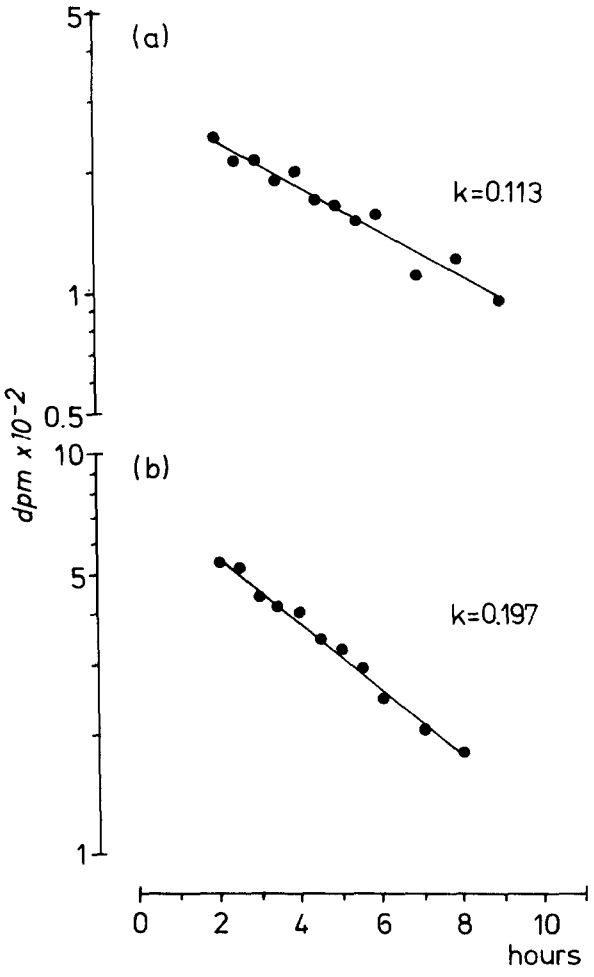

Fig. 1. Plasma radioactivity curve after intravenous injection of [^{3}H]glycerol in patient no. 4 (EH) before (*a*) and during (*b*) treatment with cholestyramine, 12 g daily. The computed apparent fractional turnover rate constants (*k*) are indicated in the figure. The plasma triglyceride concentration was 1.9 mmol/l before and 1.2 mmol/l during therapy (cf. Table 3).

RESULTS

Treatment with cholestyramine

Individual values for plasma lipid levels and the apparent fractional turnover rate and synthesis of endogenous plasma triglyceride are listed in **Table 3.**

In type II HLP the cholesterol levels decreased in all subjects, on the average from 8.2 ± 0.3 to 6.3 ± 0.4 mmol/l ($P < 0.001$). The plasma concentration of triglycerides remained constant, but the apparent fractional turnover rate, as determined over 10 hr, increased in all patients. The means encountered before (0.176 ± 0.014 hr^{-1}) and during treatment (0.230 ± 0.017 hr^{-1}) differed by about 30% ($P < 0.001$). These changes were associated in all instances with an elevation of the apparent plasma triglyceride formation (from 9.7 ± 1.2 to 12.8 ± 1.5 μmol $kg^{-1}hr^{-1}$, $P < 0.005$). The plasma radioactivity decay curves of a representative patient before and during treatment are shown in **Fig. 1.** The highest value for plasma triglyceride synthesis, both before and during medication, was found in the patient with the type IIb lipoprotein pattern.

The mean apparent formation of endogenous plasma triglycerides in patients with type IV HLP was about twice as high as that encountered in type II. Treatment with cholestyramine had no consistent effect on the plasma concentrations of cholesterol and triglycerides, and no significant effects on apparent plasma tryglyceride fractional turnover rate or synthesis were seen (Table 3).

Treatment with chenodeoxycholic acid

The values recorded for the levels of plasma cholesterol and triglycerides and the kinetics of plasma triglycerides as determined over a 10-hr period under basal conditions were similar to those recorded for the patients treated with cholestyramine (**Table 4**). The response to therapy with the two drugs was found to differ markedly. During treatment with CD the plasma levels of cholesterol remained unchanged, while those of triglycerides decreased in three of the patients with type II and in six of those with type IV HLP, the changes reaching statistical significance in type IV HLP and in the combined series of patients (2.4 ± 0.4 vs. 2.8 ± 0.4 mmol/l, $P < 0.02$). The apparent formation of endogenous plasma triglycerides decreased in all patients with type IIa HLP (from 13.1 ± 1.2 to 7.9 ± 0.5 μmol $kg^{-1}hr^{-1}$, $P < 0.01$) and in six of the seven subjects with type IV HLP (from 23.9 ± 3.8 to 15.3 ± 1.9 μmol $kg^{-1}hr^{-1}$, $P < 0.02$). The apparent fractional turnover rate of plasma triglycerides as determined over 10 hr was lower during CD treatment in all patients with type IIa and in five of those with type IV HLP (Table 4). **Fig. 2** displays the changes in triglyceride kinetics in one patient with type IV HLP.

DISCUSSION

It is well documented that interruption of the enterohepatic circulation of bile acids by anion-exchange resins such as cholestyramine and colestipol promotes changes in bile acid, cholesterol, and lipoprotein metabolism. The increased formation of bile acids in HLP type II during such therapy is mainly accounted for by an augmented production of cholic acid (C), whereby the ratio of the two primary bile acids synthesized returns to normal (12). These changes are associated with enhanced cholesterogenesis (13–16, 26) and an

TABLE 4. Effect of chenodeoxycholic acid on plasma lipid levels and triglyceride kinetics in patients with hyperlipoproteinemia

Patient, Type of Hyperlipoproteinemia	Plasma Cholesterol[a]		Plasma Triglyceride[a]					
			Concentration		Apparent Fractional Turnover Rate		Apparent Turnover Rate	
	Before	During	Before	During	Before	During	Before	During
	mmol/l		*mmol/l*		*hr*$^{-1}$		*μmol/kg/hr*	
1. IIa	8.5	7.6	1.5	1.0	0.218	0.177	14.7	8.0
2. IIa	8.7	8.7	2.0	2.2	0.147	0.063	13.1	6.2
3. IIa	8.5	9.1	1.2	1.3	0.159	0.125	8.6	7.3
4. IIa	8.9	8.5	1.5	1.2	0.206	0.175	13.9	9.4
5. IIa	9.5	10.4	1.6	1.2	0.232	0.175	15.5	8.5
Mean	8.8	8.9	1.6	1.4	0.192	0.143	13.1	7.9
± SEM	± 0.2	± 0.5	± 0.1	± 0.2	± 0.017	± 0.022[f]	± 1.2	± 0.5[f]
6. IV	5.8	5.9	3.8	2.9	0.210	0.179	35.8	23.3
7. IV	5.4	5.6	2.1	1.8	0.163	0.124	15.4	10.1
8. IV	7.2	7.7	4.3	4.1	0.063	0.073	11.5	12.5
9. IV	6.5	6.5	5.3	5.5	0.163	0.088	36.6	20.3
10. IV	8.6	8.0	4.1	2.8	0.167	0.101	28.5	11.6
11. IV	5.4	6.4	2.7	2.1	0.152	0.146	16.1	12.1
12. IV	6.9	6.6	3.7	2.3	0.149	0.173	23.2	17.2
Mean	6.6	6.7	3.7	3.1	0.152	0.126	23.9	15.3
± SEM	± 0.4	± 0.3	± 0.4	± 0.5[b]	± 0.017	± 0.016	± 3.8	± 1.9[e]
Total			2.8	2.4	0.169	0.133	19.4	12.2
			± 0.4	± 0.4[e]	± 0.013	± 0.013[c]	± 2.7	± 1.6[d]

[a] To convert mmol/l to mg/dl multiply cholesterol concentrations by 38.7 and triglyceride concentrations by 0.1 × mol wt of triglyceride (e.g., 88.5 for triolein).
[b] Significantly different from pretreatment value, $P < 0.05$.
[c] Significantly different from pretreatment value, $P < 0.005$.
[d] Significantly different from pretreatment value, $P < 0.001$.
[e] Significantly different from pretreatment value, $P < 0.02$.
[f] Significantly different from pretreatment value, $P < 0.01$.

elevation of the fractional catabolic rate of low density lipoprotein (LDL) (27). The LDL level in plasma is reported to decrease, whereas that of very low density lipoprotein (VLDL) may increase (28–30). With the limitations inherent to the technique used for determination of plasma triglyceride kinetics (4, cf. Methods), the results of the present study suggest that the latter effect may be related to an increased formation of endogenous triglycerides. In accordance with our results, Nestel and Grundy (31) recently observed that the withdrawal of bile from the enterohepatic circulation is associated with an increase in the pool size and probably also with the turnover of VLDL triglycerides.

The origin of the increased amount of triglycerides that appears to be secreted into the circulation during treatment of type II HLP with cholestyramine cannot be determined presently. The possibility of an elevated intestinal synthesis of VLDL must be kept in mind, although cholestyramine appears to inhibit VLDL formation in the mucosal cells of the rat (32). In the liver, cholesterol and bile acid formation are stimulated by cholestyramine, and it is probable that the newly formed cholesterol is delivered from the liver both as bile acids and as cholesterol in VLDL. As mentioned, in HLP type IIa cholestyramine treatment stimulates the formation of C to a greater extent than that of CD (12). Patients with type IV HLP, who often have an abnormally high formation of bile acids, especially C (3, 4), did not show any further increase in C production during treatment with cholestyramine (12). It is of interest to note that these patients did not exhibit any significant change in triglyceride formation. However, type IV HLP is of heterogenous origin, and some previous reports indicate that the VLDL level may increase during therapy (28, 30).

CD treatment results in an inhibited rate of conversion of cholesterol to bile acids (10, 17, 20) and interferes with hepatic cholesterogenesis (33).[1] The plasma triglyceride level is reported to decline slightly in patients with cholelithiasis (33–35) and to a greater degree in subjects with hypertriglyceridemia due to HLP type IIb, IV, or V (36, 37). Again with some reservation with regard to the possible errors of the

[1] Ahlberg, J., B. Angelin, and K. Einarsson. Manuscript in preparation.

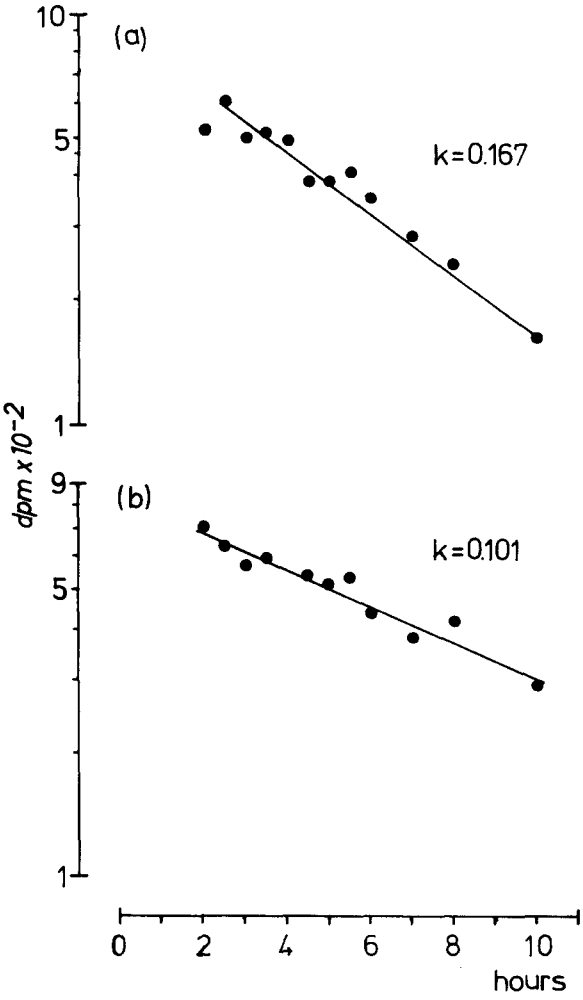

Fig. 2. Plasma radioactivity curve after intravenous injection of [^{3}H]glycerol in patient no. 10 (TL) before (*a*) and during (*b*) treatment with chenodeoxycholic acid, 1.9 mmol daily. The computed apparent fractional turnover rate constants (*k*) are indicated in the figure. The plasma triglyceride concentration was 4.1 mmol/l before and 2.8 mmol/l during therapy (cf. Table 4).

method used, the results of the present investigation suggest that this is due to a reduced formation of endogenous plasma triglycerides. The apparent synthesis of triglyceride decreased about 35% in both type IIa and type IV HLP, whereas the drop in plasma triglyceride concentration was more moderate. Before and during administration of CD to the present patients, the apparent biosynthesis of plasma triglycerides as determined over 10 hr in those with HLP type IV exceeded that encountered in the subjects with HLP type II. A similar difference between these types of HLP with regard to the production of C before and during treatment with CD was observed by Kallner (20).

Thus, the results of the present study support the view that changes in the formation of plasma (VLDL) triglycerides and bile acids occur in parallel. Furthermore, experimental conditions primarily altering the metabolism of bile acids seem to affect that of plasma triglycerides as well. It is difficult to explain these observations from the viewpoint that the bile acids are *only* the end-point of lipoprotein cholesterol. Instead, as discussed previously (4), a regulatorily important pool of hepatic cholesterol may be hypothesized to form the linkage between bile acid and lipoprotein metabolism. In view of the present study, the possibility of a defective intestinal uptake of C, as has been suggested in some patients with type IV HLP (3,38,39); as a regulatory factor affecting plasma triglyceride metabolism must also be considered.

During treatment with cholestyramine the apparent plasma triglyceride fractional turnover rate as determined over 10 hr was enhanced in type II HLP, whereas it showed a decrease during administration of CD. These changes—even if they should only pertain to the first, rapid part of a multicompartmental decay curve (cf. Methods)—do suggest an acceleration of VLDL turnover during cholestyramine treatment and a slower elimination of the lipoprotein particle during medication with CD. Removal of VLDL triglyceride is generally thought to occur in peripheral tissues through the action of lipoprotein lipase (40), and the possibility that alterations in lipase activities are at least in part responsible for the changes in apparent fractional turnover rate must of course be considered.[2] Another possible explanation is that the changes observed monitor differences in the composition and size of the lipoproteins secreted.

In conclusion, the results of the present investigation suggest that experimental conditions primarily altering the metabolism of bile acids affect that of plasma triglycerides in parallel. More detailed studies on lipoprotein metabolism during perturbed bile acid and cholesterol turnover appear to be of definite future interest.

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[2] It may be speculated that such possible effects could be mediated via changing serum bile acid levels. During treatment with CD, there is a threefold increase in peripheral venous serum bile acid concentration (Ahlberg, J., B. Angelin, I. Björkhem, K. Einarsson, and S. Ewerth, unpublished data).

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