Plasma fatty acids and [^{13}C]linoleic acid metabolism in preterm infants fed a formula with medium-chain triglycerides

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Abstract **Most preterm infant formulas contain medium-chain triacylglycerols (MCT), but the effects of MCT on polyunsaturated fatty acid status and metabolism are controversial. Thus, we studied the effects of MCT on linoleic acid metabolism using stable isotopes. Enterally fed preterm infants were randomized to receive for 7 days 40% of fat as MCT (n = 10) or a formula without MCT (n = 9). At study day 5, infants received orally 2 mg/kg body weight of ^{13}C-labeled linoleic acid. Fatty acids in plasma lipid classes and ^{13}C enrichment of phospholipid fatty acids were measured and tracer oxidation was monitored. Compared with the control group, the MCT group showed lower breath $^{13}CO_2$ and higher plasma triacylglycerol contents of octanoic acid, of decanoic acid, and of total long-chain polyunsaturated fatty acids (57.1 ± 4.4 μmol/l vs. 37.9 ± 4.8 μmol/l, $P < 0.01$). Concentrations of several polyunsaturated fatty acids in plasma phospholipids and non esterified fatty acids were higher in the MCT group. ^{13}C concentrations in phospholipid n-6 fatty acids indicated no difference in the relative conversion of linoleic to arachidonic acid. We conclude that oral MCT effectively reduce polyunsaturated fatty acid and long chain polyunsaturated fatty acid oxidation in preterm infants without compromising endogenous n-6 long chain polyunsaturated fatty acid synthesis.—** Rodriguez, M., S. Kiss, M. Fink, H. Demmelmair, M. Turini, G. Crozier, and B. Koletzko. **Plasma fatty acids and [^{13}C]linoleic acid metabolism in preterm infants fed a formula with medium-chain triglycerides. *J. Lipid Res.* 2003.** 44: **41–48.**

Supplementary key words long chain polyunsaturated fatty acid • tracer • long-chain triacylglycerols • LCT • fatty acid oxidation

Preterm infant formulas are considered the best substitute for those premature infants who cannot receive sufficient amounts of human milk. The fat blend of preterm formulas contains up to 50% medium-chain fatty acids (8:0, 10:0; MCT) usually contributed by coconut oil (1). They are added to enhance fat and calcium absorption and to provide the premature infant with a readily available source of energy (2, 3). In addition, oral lipid supplementation containing a high percentage of MCT was shown to prevent the occurrence of hypoglycemia in low birth weight infants (4). In comparison to long-chain triacylglycerols (LCT), MCT are more efficiently absorbed in the digestive tract, and the liberated medium chain fatty acids (MCFA) are extensively and rapidly oxidized, whereas long chain fatty acids (LCFA) are largely stored in tissues (5). The intense lipid oxidation is associated with a ketogenic effect of dietary MCT, which provides an alternative energy source and is considered harmless for the infant as long as ketone body concentrations do not exceed values observed in breast fed infants (5, 6).

Recent studies using stable isotopes have demonstrated that preterm infants are able to synthesize long-chain polyunsaturated fatty acids (LCP) such as arachidonic (20:4n-6) and docosahexaenoic acids (22:6n-3) from their precursor fatty acids, linoleic (18:2n-6) and α-linolenic acids (18:3n-3) (7). Ingestion of MCT is associated with profound changes in plasma fatty acid composition (8, 9), but the effects of MCT on essential fatty acid and LCP status are controversial. Wall et al. (10) found significantly lower tissue levels of arachidonic acid in new-born piglets fed infant formulas containing MCT than in piglets fed formulas containing coconut oil (12:0 + 14:0). In premature infants, an interference of MCT on LCP metabolism was suggested by Carnielli et al. (9), who reported no effect on 20:4n-6 concentrations but a decrease in plasma phospholipid 22:6n-3 concentrations after MCT feeding.

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Abbreviations: AP, atom percent; APE, atom percent excess; LCFA, long chain fatty acid; LCP, long chain polyunsaturated fatty acids; LCT, long chain triacylglycerol; MCFA, medium chain fatty acids (8:0–12:0); MCT, medium chain triacylglycerols (8:0–12:0); MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

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On the other hand, the oxidation of MCT in liver creates a readily available source of reducing equivalents and of carbon precursors that could foster elongation of fatty acids (11). In addition, mRNA concentrations and activities of lipogenic enzymes increase with MCT feeding in contrast to the inhibition seen with LCT feeding (12). Periago et al. have shown in rats that inclusion of MCT in the diet caused increased LCP in erythrocyte membrane phospholipids (13).

Adequate brain and tissue levels of 20:4n-6 and 22:6n-3 are important for optimal growth and neuronal development, particularly in preterm infants (14, 15). The 20:4n-6 supply has been associated with gain in weight (16) and body length (17), and 22:6n-3 availability has been associated with higher scores in cognitive and visual tests (18–22). Therefore, whether MCT interferes with essential fatty acid metabolism in infants is of considerable interest. In the present study, we investigated the effect of dietary MCT on plasma fatty acid composition, LCP status, and n-6 fatty acid metabolism in premature infants using uniformly ^{13}C-labeled 18:2n-6.

TABLE 1. Fatty acid composition of the study formulas

	Control	MCT
	% *wt/wt*	
Saturated fatty acids		
8:0	0.09	22.24
10:0	0.13	17.63
12:0	0.32	0.28
14:0	1.45	0.88
16:0	39.91	20.16
18:0	4.71	2.84
20:0	0.45	0.26
22:0	0.15	0.12
Other	0.30	0.21
Monounsaturated fatty acids		
18:1n-9	36.24	21.24
18:1n-7	0.95	0.57
Other	0.49	0.30
Polyunsaturated fatty acids		
18:2n-6	13.15	11.87
18:3n-3	1.03	1.13
20:4n-6	0.01	0.01
22:6n-3	0.00	0.00
Total n-6PUFA	13.28	11.98
Total n-3PUFA	1.03	1.13
trans fatty acids		
Total	0.47	0.14

SUBJECTS AND METHODS

Prematurely born (gestational age <37 weeks), but otherwise healthy infants were enrolled into the study at the Division of Neonatology, University of Pécs, Hungary. Inclusion criteria for the study were birth weight between 1,000 g and 2,000 g, weight appropriate for gestational age (10th to 90th percentile), exclusive formula feeding with a minimal daily ingestion of 100 ml/kg body weight, good and stable clinical condition, and no use of intravenous lipid emulsions at the time of enrolment. The study protocol was approved by the ethical committee, University of Pécs and written informed consent was obtained from the parents of all infants after detailed description of the study aim and methods.

Infants were randomized to two feeding groups; one received a formula with 40% (w/w) MCT in dietary fat (MCT group), whereas the other group was fed a formula with negligible contents of MCFA (control group; **Table 1**). The omission of MCFA in the control formula was mainly balanced by palmitic and oleic acid, but in addition to that, the linoleic acid content was slightly higher in the control formula (13.15% vs. 11.87%). Contents of macronutrients (protein, 11.4%; carbohydrates, 39.9%; fat, 46.7% of total energy) and micronutrients were identical in both groups. The study diet was fed for 7 days. On day 5, after introducing the study formulas, 2 mg/kg birth weight of uniformly ^{13}C-labeled (98%) 18:2n-6 (Martek Bioscience, Columbia, MD) was given orally to the infants as free fatty acid. The tracer was dissolved in a small amount of the corresponding formula and was given to the infants immediately prior to feeding.

Methods

Breath samples were obtained before and at 30-min intervals after tracer application over a 6 h-period. Using a subnasal prong connected via a 3-way valve to a 20 ml syringe, exhaled breath was manually aspirated during the second half of the expiratory phase and transferred into vacutainers (10 ml, Labco Ltd., Wycombe, UK). Samples obtained before the application of labeled 18:2n-6 were used as baseline values to measure the natural ^{13}C enrichment in breath samples. ^{13}C-analyses of breath CO_2 were performed by isotope ratio mass spectrometry (23).

Blood samples were obtained before tracer intake on the fifth study day, and 24 h and 48 h after tracer application. Samples were collected into EDTA-containing tubes. After centrifugation (10 min, at 1,300 *g*), plasma was removed and stored at −80°C until analysis. Internal standards [dinonanoyl phosphatidylcholine, trinonanoin, and nonanoic acid for quantification of MCFA; dipentadecanoyl phosphatidylcholine, tripentadecanoin, pentadecanoic acid for quantification of LCFA (Sigma, St Louis, MO)] were added to 250 μl plasma. Lipids were then extracted once with 2 ml hexane-isopropanol, 4:1 (v/v/v), and twice with 2 ml hexane, and the pooled extracts were dried under nitrogen and redissolved in chloroform. Separation of the lipid classes was performed by thin layer chromatography using a mixture of heptane-isopropanol-acetic acid 60:40:3 (v/v/v) as mobile phase. Lipid classes (phospholipids, triacylglycerols and free fatty acids) were transesterified with 2 ml 1.5 M methanolic hydrochloric acid (Supelco, Deisenhofen, Germany), 1 ml methanol, and 0.5 ml hexane at 80°C for 1 h. After neutralization, distilled water was added, and the organic phase was transferred into a crimp capped storage vial. Recoveries of about 90% were obtained for MCFA (data not shown) by avoiding concentrating the methyl ester solution.

Quantitative analysis of fatty acid methyl esters was performed with a Hewlett-Packard 5890 series II GC (Hewlett Packard, Waldbronn, Germany) equipped with an autosampler and a flame ionization detector. Separation of the individual fatty acids was accomplished with a 60 m × 0.32 mm BPX 70 column (SGE, Weiterstadt, Germany) and splitless injection using the given temperature program: start at 45°C for 0.5 min, temperature increase of 6°C/min until 150°C, followed by a second rate of 3°C/min until 190°C, and a third rate of 0.5°C/min until the final temperature of 201°C. Injector and detector temperatures were 250°C and 300°C, respectively. Commercial standards (Sigma; NuChek, Malysian, MN) were used for the identification of individual fatty acids and the determination of response factors. In a further aliquot of the fatty acid methyl esters solution derived from the plasma phospholipid fraction, ^{13}C content of individual fatty acid methyl esters was determined by gas chromatography-combustion-isotope ratio mass spectrometry (delta S, Finnigan MAT, Bremen, Germany) as previously described (24). Samples were analyzed in duplicate and results are expressed as ^{13}C atom percentage (AP).

Plasma β-hydroxybutyrate concentrations were determined enzymatically (Sigma Diagnostics, St Louis, MO).

Calculations

The increase in ^{13}C content above baseline (atom percent excess, APE %) was obtained by subtracting the basal AP values measured before tracer application from the AP values measured after tracer application.

Absolute tracer concentrations in plasma phospholipid fatty acids (μmol ^{13}C/l) were calculated by the following equation:

$$^{13}CFA = \mu mol\ FA * n * APE / 100 \qquad (Eq.\ 1)$$

where μmol FA is the plasma fatty acid concentration in μmol/l and n is the number of carbon atoms of the methylated fatty acid (number of carbon atoms of the fatty acid + 1). Additionally, the ratios between ^{13}C concentrations in 18:2n-6, 20:3n-6, and 20:4n-6 were calculated as an indicator of the conversion intensity.

Statistical analysis

All statistical calculations were performed with SPSS (SPSS, v. 8.0, Chicago, IL). Since plasma fatty acid concentrations from study days 5, 6, and 7 were not significantly different, these values were averaged for each individual and means were used for statistical comparisons between groups. Results are given as means and standard errors of the mean (SEM). All data were examined for normality and variance homogeneity before statistical analysis. Differences between the feeding groups were evaluated by the non-parametric U-Mann-Whitney test. $P \leq 0.05$ were considered statistically significant.

RESULTS

A total of 19 preterm infants participated in the study; nine infants were assigned to the control group and 10 infants to the MCT group. Infants in the two study groups presented similar clinical characteristics at birth and at the time of tracer application, on study day 5 (**Table 2**). No adverse effects associated with the ingestion of the two formulas were observed during the study. Most infants had received intravenous infusions containing amino acids and lipids until the 6th day of life, and only one patient had received lipid emulsions until the 12th day of life. During the study period, no infant received intravenous lipid emulsions. Blood samples from five infants in the control group and two infants in the MCT group were not obtained at the last study day and for that reason, fatty acid concentrations and ^{13}C-enrichment 48 h after tracer application was not available in these subjects.

TABLE 2. Clinical characteristics [mean (SEM)] of infants at birth and at study day 5

	Control (n = 9)	MCT (n = 10)
Birth characteristics		
Gestational age (wk)	30 (0.8)	31 (0.6)
Weight (g)	1370.0 (94.1)	1457.0 (55.0)
Height (cm)	39.4 (0.9)	40.1 (0.6)
Head circumference (cm)	27.8 (0.5)	28.5 (0.2)
Study day 5		
Postnatal age (d)	35 (4.6)	35 (4.5)
Weight (g)	1823.3 (88.6)	1913.0 (88.1)
Height (cm)	43.3 (0.5)	44.1 (0.7)
Energy intake (kcal/kg/d)	122.8 (5.1)	137.0 (5.7)
Weight gain from birth ($g \cdot kg^{-1} \cdot d^{-1}$)	17.3 (5.5)	16.1 (3.5)
Tracer ingested (mg/kg)	2.3 (0.1)	2.2 (0.1)

At all measuring points, infants ingesting the control formula showed higher breath APE values than infants ingesting the formula with MCT (**Fig. 1**).

In comparison with the control group, the MCT group showed significantly higher amounts of 8:0+10:0 in plasma triacylglycerols (315.3 ± 41.5 μmol/l vs. 16.5 ± 4.7 μmol/l, $P < 0.01$, **Table 3**). The concentrations of all detected fatty acids (with the exception of oleic acid) in triacylglycerols were significantly higher or tended to be higher in the MCT group, but total triacylglycerol fatty acid concentration was not significantly higher in the MCT group. Nevertheless, it showed a strong tendency to do so. The relative distribution of fatty acids was shifted toward significantly higher MCFA and 18:3n-3, while the percentages of palmitic and oleic acid was significantly lower in the MCT group.

The significantly higher concentration of total non esterified fatty acids was mainly caused by the more than three times higher levels of 8:0+10:0 in the MCT group (182.0 ± 19.2 μmol/l vs. 51.34 ± 6.0 μmol/l, $P < 0.01$, **Table 4**), while palmitic, oleic and linoleic acid concentra-

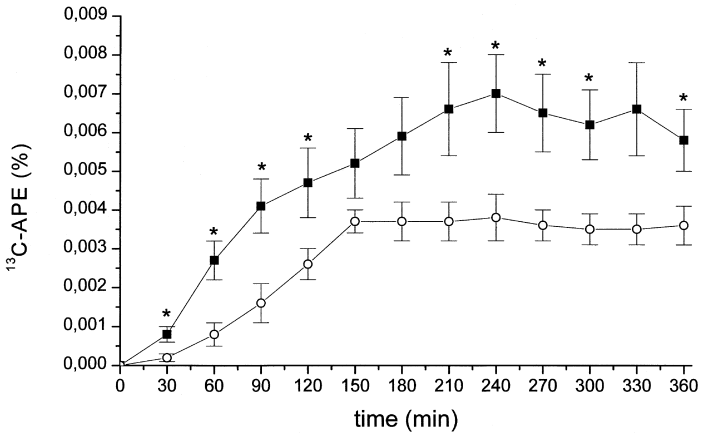

Fig. 1. ^{13}C-atom percent excess values (means + SEM) in breath CO_2 measured over 6 h after tracer application in preterm infants fed control (black columns) or medium chain triacylglycerols (8:0–12:0) (MCT) (white columns) formula. *$P < 0.05$.

TABLE 3. Fatty acid composition of plasma triacylglycerols in preterm infants fed control and MCT formulas

	Relative Values		Absolute Values	
	Control (n = 9)	MCT (n = 10)	Control (n = 9)	MCT (n = 10)
	mol %		*μmol/l*	
Saturated fatty acids				
8:0	0.35 (0.12)	2.97 (0.23)[b]	7.35 (2.09)	93.79 (12.73)[b]
10:0	0.46 (0.18)	7.03 (0.54)[b]	9.15 (2.78)	221.50 (29.41)[b]
12:0	0.07 (0.03)	0.05 (0.01)	1.31 (0.46)	1.48 (0.26)
14:0	1.57 (0.09)	2.25 (0.10)[b]	37.65 (3.18)	67.55 (6.02)[b]
16:0	30.81 (0.79)	27.22 (0.75)[b]	738.38 (42.35)	839.01 (94.81)
17:0	0.17 (0.01)	0.18 (0.01)	4.11 (0.28)	5.36 (0.52)
18:0	3.20 (0.21)	3.67 (0.11)	75.09 (4.00)	112.21 (11.79)[b]
20:0	0.20 (0.01)	0.21 (0.01)	4.60 (0.25)	6.22 (0.59)[a]
22:0	0.06 (0.01)	0.08 (0.01)[a]	1.36 (0.11)	2.48 (0.33)[b]
Σ SFA	36.88 (1.04)	43.66 (1.28)[b]	879.00 (47.68)	1349.61 (148.95)[a]
Monounsaturated fatty acids				
14:1n-5	0.11 (0.01)	0.16 (0.01)[a]	2.56 (0.13)	4.47 (0.26)[b]
16:1n-7	2.64 (0.39)	3.69 (0.55)	65.07 (11.26)	106.82 (14.41)[a]
18:1n-9	42.85 (0.66)	32.85 (0.63)[b]	1030.58 (71.44)	1004.04 (107.36)
18:1n-7	1.89 (0.17)	2.22 (0.21)	46.08 (5.68)	65.17 (6.07)[a]
20:1n-9	0.40 (0.01)	0.45 (0.02)[a]	9.78 (0.78)	13.71 (1.31)[a]
Σ MUFA	47.90 (0.95)	39.37 (1.03)[b]	1154.07 (84.77)	1194.21 (115.67)
Polyunsaturated fatty acids				
20:3n-9	0.20 (0.02)	0.31 (0.05)	4.84 (0.64)	8.59 (0.83)[b]
n-6 PUFA				
18:2n-6	12.41 (0.13)	13.28 (1.06)	296.79 (16.18)	411.31 (57.98)
18:3n-6	0.22 (0.02)	0.27 (0.02)	5.39 (0.71)	7.50 (0.38)
20:2n-6	0.17 (0.01)	0.25 (0.02)[b]	3.99 (0.32)	7.66 (1.08)[b]
20:3n-6	0.22 (0.02)	0.21 (0.02)	5.15 (0.51)	6.18 (0.65)
20:4n-6	0.49 (0.06)	0.54 (0.05)	11.83 (1.59)	15.49 (1.24)
22:4n-6	0.11 (0.01)	0.14 (0.01)	2.59 (0.43)	3.98 (0.31)[a]
22:5n-6	0.15 (0.02)	0.22 (0.03)[a]	3.57 (0.58)	6.53 (0.81)[a]
n-6 PUFA	13.77 (0.17)	14.91 (1.10)	329.29 (18.93)	458.65 (60.85)
n-6 LCP	1.13 (0.11)	1.36 (0.11)	27.12 (3.33)	39.84 (3.62)[a]
n-3 PUFA				
18:3n-3	0.75 (0.03)	1.05 (0.08)[b]	17.73 (0.82)	33.32 (5.10)[a]
20:5n-3	0.05 (0.00)	0.08 (0.01)[b]	1.14 (0.14)	2.28 (0.08)[b]
22:5n-3	0.08 (0.01)	0.08 (0.01)	1.90 (0.31)	2.50 (0.28)
22:6n-3	0.12 (0.02)	0.13 (0.01)	2.94 (0.48)	3.86 (0.43)
n-3 PUFA	0.99 (0.03)	1.35 (0.08)[b]	23.70 (1.20)	41.96 (5.68)[b]
n-3 LCP	0.25 (0.03)	0.30 (0.02)	5.97 (0.86)	8.64 (0.72)[a]
Σ PUFA	14.96 (0.20)	16.57 (1.16)[a]	357.83 (20.54)	509.20 (65.95)
Σ LCP	1.59 (0.16)	1.97 (0.16)	37.93 (4.75)	57.07 (4.36)[a]
Σ fatty acids			2396.61 (144.75)	3064.75 (312.93)

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; LCP, long-chain polyunsaturated fatty acids. Values are means and SEM.

[a] $P < 0.05$.

[b] $P < 0.01$.

tions were comparable in both groups. Therefore, percentage values of most fatty acids with more than 10 carbon atoms were significantly lower (Table 4).

In contrast to the other fractions, phospholipid fatty acids hardly differed in their concentrations between groups, as there was no detectable incorporation of MCFA into phospholipids. Oleic acid percentage was significantly higher in the control group, while 18:3n-3 was lower (**Table 5**).

Ingestion of the formula enriched with MCT was associated with higher contents of polyunsaturated fatty acids of both n-6 and n-3 series in the three lipid fractions studied, although the largest differences were observed in the triacylglycerol fraction, where total LCP concentration was 57.1 ± 4.4 μmol/l in the MCT group compared with 37.9 ± 4.8 μmol/l in the control group ($P < 0.05$) (Tables 3–5).

The plasma concentrations of β-hydroxybutyrate tended to be higher in the MCT-group than in the control group (0.16 ± 0.03 mmol/l vs. 0.08 ± 0.01 mmol/l, not significant).

Figure 2 shows the ^{13}C concentrations (μmol/l) in plasma phospholipid 18:2n-6 and its longer chain metabolites at 24h and at 48h (as available) after tracer administration. In both groups, plasma phospholipid 18:2n-6 showed maximal enrichment 24 h after tracer application and decreased markedly until 48 h. ^{13}C enrichments in dihomo-γ-linolenic acid (20:3n-6) and arachidonic acid (20:4n-6) increased moderately from baseline to 24 h after tracer application, and showed little change until 48 h. The plasma phospholipid ^{13}C concentrations in μmol/l tended to be lower (not significant) in the MCT group. The ratios between product (20:4n-6) and precursor (18:2n-6) tracer concentrations, which indicate conversion intensity toward n-6 LCP, were similar in both groups 24 h after tracer intake (0.026 ± 0.005 vs. 0.029 ± 0.005, control vs. MCT) and 48 h afterwards (0.085 ± 0.013 vs. 0.107 ± 0.016). Furthermore, there were no significant differences between groups in all other calculated tracer ratios: 20:3n-6/18:2n-6, 20:4n-6/

TABLE 4. Fatty acid composition of plasma non esterified fatty acids in preterm infants fed control and MCT formulas

	Relative Values		Absolute Values	
	Control (n = 9)	MCT (n = 10)	Control (n = 9)	MCT (n = 10)
	mol %		*μmol/l*	
Saturated fatty acids				
8:0	8.78 (1.41)	23.77 (1.92)[b]	21.48 (3.91)	98.04 (13.29)
10:0	12.46 (0.73)	21.69 (0.85)[b]	29.90 (2.63)	83.99 (6.83)[b]
12:0	0.16 (0.01)	0.16 (0.02)	0.38 (0.04)	0.62 (0.12)
14:0	1.85 (0.06)	1.63 (0.08)	4.46 (0.24)	6.32 (0.83)[b]
16:0	31.31 (0.59)	22.89 (1.02)[b]	76.33 (4.53)	88.18 (10.44)
18:0	9.04 (0.44)	6.57 (0.33)[b]	21.64 (1.03)	25.28 (3.27)
Σ SFA	63.60 (1.16)	76.70 (1.33)[b]	154.20 (9.21)	302.43 (29.50)[b]
Monounsaturated fatty acids				
16:1n-7	1.09 (0.12)	0.88 (0.11)	2.66 (0.30)	3.23 (0.35)
18:1n-9	21.70 (0.96)	11.52 (0.77)[b]	53.51 (3.97)	43.70 (4.12)
18:1n-7	0.89 (0.06)	0.69 (0.06)[a]	2.19 (0.19)	2.60 (0.27)
20:1n-9	2.44 (0.19)	2.35 (0.21)	5.80 (0.53)	8.88 (1.34)[a]
Σ MUFA	26.12 (0.88)	15.44 (0.78)[b]	64.16 (4.38)	58.41 (5.37)
Polyunsaturated fatty acids				
n-6 PUFA				
18:2n-6	7.92 (0.48)	5.95 (0.53)[a]	19.33 (1.51)	22.74 (2.68)
20:3n-6	0.47 (0.05)	0.36 (0.03)	1.11 (0.11)	1.36 (0.15)
20:4n-6	0.96 (0.11)	0.68 (0.09)[a]	2.27 (0.23)	2.51 (0.29)
n-6 PUFA	9.35 (0.60)	6.99 (0.54)[a]	22.71 (1.69)	26.62 (2.88)
n-6 LCP	1.43 (0.16)	1.04 (0.10)[a]	3.38 (0.33)	3.88 (0.36)
n-3 PUFA				
18:3n-3	0.39 (0.02)	0.36 (0.03)	0.96 (0.08)	1.38 (0.14)[a]
n-3 PUFA	0.39 (0.02)	0.36 (0.03)	0.96 (0.08)	1.38 (0.14)[a]
Σ PUFA	9.74 (0.61)	7.35 (0.57)[a]	23.67 (1.74)	28.00 (3.00)
Σ LCP	1.43 (0.16)	1.04 (0.10)[a]	3.38 (0.33)	3.88 (0.36)
Σ fatty acids	100.00 (0.00)	100.00 (0.00)	243.35 (13.20)	390.87 (36.45)[b]

Values are means and SEM. SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; LCP, long-chain polyunsaturated fatty acids.

[a] $P < 0.05$.

[b] $P < 0.01$.

20:3n-6 and (20:3n-6+20:4n-6)/18:2n-6. All product/precursor ratios were higher at 48 h than at 24 h after intake.

DISCUSSION

The significantly lower APE values of exhaled CO_2 in the MCT group indicate that the exogenously applied ^{13}C-labeled 18:2n-6 contributed less to total substrate oxidation in the MCT group than in the LCT group during the postprandial phase. Liet et al. demonstrated that total CO_2 production is not significantly different between preterm neonates fed parenterally with an LCT or an MCT/LCT emulsion (25). As the 18:2n-6 content was slightly lower in the MCT formula, a higher dilution of the tracer within the diet can be excluded. Thus, one explanation for the difference in $^{13}CO_2$ enrichment is a lower 18:2n-6 oxidation rate in the MCT group. On the other hand, triacylglycerol bound 18:2n-6 was about one third higher in the MCT group, causing a higher dilution of the ingested tracer in the present pool of 18:2n-6 and as a consequence less tracer was oxidized. Both explanations are in agreement, as relatively less oxidation of dietary 18:2n-6 leads to higher plasma concentrations, which by itself decreases trace recovery in breath. Differences in intestinal tracer absorption are not expected as similar percentage absorption of individual fatty acids have been reported in infants receiving formulas providing fat as LCT or as MCT (26), and it can reasonably be assumed that ^{13}C-labeled 18:2n-6 was efficiently absorbed in both groups. Preferential MCFA oxidation by the liver in the postprandial phase influences 18:2n-6 oxidation in infants fed the formula with MCT. After absorption, LCFA are mostly reesterified into triacylglycerols in the intestinal epithelial cells to form chylomicrons that are transported via the lymph and taken to all tissues, whereas MCFA are largely transported via the portal vein and reach the liver as the first organ perfused. In the hepatocyte, LCFA are preferentially activated in the cytosol and incorporated into triacylglycerols and phospholipids, and only a small proportion enters the mitochondria via the carnitine acyltransferase system. On the other hand, MCFA may enter the mitochondria partially independent from carnitine and are largely oxidized (5). It has been shown that during MCT ingestion the carnitine palmitoyltransferase is inhibited, consequently oxidation of LCFA is reduced and their incorporation into complex lipids enhanced (27). These metabolic differences between MCT and LCT explain why in preterm infants fed a high MCT diet, the preferential oxidation of MCFA causes a decrease in 18:2n-6 oxidation.

Although the oxidation rate of MCFA is much higher than that of LCFA (28), the study by Sulkers et al. (29) shows that about half of the ingested MCT follows pathways other than oxidation. Among these, urinary loss of dicarboxylic acids,

TABLE 5. Fatty acid composition of plasma phospholipids in preterm infants fed control and MCT formulas

	Relative Values		Absolute Values	
	Control (n = 9)	MCT (n = 10)	Control (n = 9)	MCT (n = 10)
	mol %		*μmol/l*	
Saturated fatty acids				
12:0	0.04 (0.01)	0.04 (0.01)	1.23 (0.17)	1.15 (0.21)
14:0	0.26 (0.02)	0.34 (0.02)[a]	8.01 (0.75)	11.11 (1.11)
16:0	29.83 (0.33)	29.90 (0.65)	937.30 (40.19)	961.16 (56.76)
17:0	0.28 (0.01)	0.31 (0.01)	8.78 (0.23)	9.83 (0.54)
18:0	15.59 (0.28)	16.12 (0.36)	487.90 (18.18)	516.74 (30.89)
20:0	0.77 (0.03)	0.77 (0.02)	24.35 (1.38)	24.71 (1.20)
22:0	1.13 (0.06)	1.19 (0.05)	35.38 (1.94)	37.85 (1.93)
24:0	0.92 (0.04)	1.03 (0.05)	28.98 (1.64)	32.59 (1.79)
Σ SFA	48.83 (0.35)	49.70 (0.55)	1531.94 (59.76)	1595.12 (87.34)
Monounsaturated fatty acids				
16:1n-7	0.47 (0.05)	0.63 (0.13)	15.01 (2.24)	20.80 (4.94)
18:1n-9	12.60 (0.20)	10.73 (0.37)[b]	396.66 (20.72)	346.02 (24.29)
18:1n-7	1.66 (0.12)	1.75 (0.16)	53.27 (5.89)	56.61 (6.69)
20:1n-9	0.34 (0.02)	0.36 (0.03)	10.80 (0.82)	11.89 (1.63)
24:1n-9	2.44 (0.19)	2.49 (0.15)	78.43 (9.62)	79.17 (5.39)
Σ MUFA	17.51 (0.41)	15.96 (0.71)[a]	554.18 (37.20)	514.50 (39.39)
Polyunsaturated fatty acids				
20:3n-9	0.39 (0.03)	0.65 (0.17)	12.37 (1.28)	21.65 (6.19)
n-6 PUFA				
18:2n-6	19.49 (0.57)	19.58 (1.08)	609.51 (24.10)	622.06 (38.51)
18:3n-6	0.15 (0.02)	0.17 (0.02)	4.84 (0.52)	5.73 (0.99)
20:2n-6	0.40 (0.02)	0.56 (0.03)	12.57 (0.89)	18.17 (1.85)[a]
20:3n-6	2.90 (0.13)	2.56 (0.15)	91.25 (6.20)	83.23 (7.76)
20:4n-6	6.61 (0.33)	6.77 (0.31)	208.96 (16.56)	218.78 (16.90)
22:2n-6	0.47 (0.04)	0.51 (0.05)	14.67 (1.01)	15.77 (1.47)
22:4n-6	0.40 (0.02)	0.41 (0.03)	12.83 (1.10)	13.66 (1.61)
22:5n-6	0.43 (0.03)	0.56 (0.04)[a]	13.41 (1.10)	18.60 (2.07)[a]
n-6 PUFA	30.85 (0.33)	31.13 (0.88)	968.03 (39.61)	996.00 (53.66)
n-6 LCP	11.21 (0.39)	11.38 (0.42)	353.68 (23.75)	368.21 (27.49)
n-3 PUFA				
18:3n-3	0.10 (0.00)	0.15 (0.01)[b]	3.06 (0.18)	4.95 (0.50)[b]
20:3n-3	0.05 (0.00)	0.06 (0.01)[a]	1.59 (0.10)	2.11 (0.24)
20:5n-3	0.19 (0.02)	0.32 (0.03)[b]	5.96 (0.84)	10.35 (1.34)[a]
22:5n-3	0.30 (0.02)	0.31 (0.02)	9.52 (0.91)	10.17 (1.00)
22:6n-3	1.50 (0.13)	1.36 (0.06)	47.63 (5.58)	43.90 (3.38)
n-3 PUFA	2.13 (0.14)	2.21 (0.07)	67.75 (6.75)	71.49 (5.28)
n-3 LCP	2.03 (0.15)	2.05 (0.06)	64.70 (6.69)	66.54 (4.88)
Σ PUFA	33.37 (0.31)	33.98 (0.75)	1048.15 (45.75)	1089.14 (58.37)
Σ LCP	13.63 (0.54)	14.08 (0.49)	430.75 (31.20)	456.40 (34.21)
Σ fatty acids	100.00 (0.00)	100.00 (0.00)	3143.38 (140.64)	3210.34 (169.38)

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; LCP, long-chain polyunsaturated fatty acids. Values are means and SEM.

[a] $P < 0.05$.

[b] $P < 0.01$.

storage in adipose tissue, and conversion to LCFA has been described (11, 27, 30). We observed a trend toward higher β-hydroxybutyrate plasma levels in the MCT group, with concentrations similar to previous observations in neonates fed formula or breast milk (31, 32, 33).

Relatively high proportions of 8:0 and 10:0 are incorporated into plasma triacylglycerols. The percentages of MCFA found in our study after MCT feeding are similar to those reported by Carnielli et al. (9). Although dietary MCFA are largely transported via the portal vein, the simultaneous ingestion of MCT and LCT may enable the lymphatic transport of MCFA (34, 35). In the present study, 8:0 was the predominant MCFA in the diet, but there was three times more 10:0 than 8:0 in plasma triacylglycerols of the infants, suggesting a decreased tendency toward oxidation or an increased tendency toward incorporation into triacylglycerols with increasing carbon chain length (36). Furthermore, during MCT feeding the oxidation capacity for MCFA by the liver might be exceeded, resulting in incomplete hepatic clearance of dietary MCFA. The production of $^{13}CO_2$ after a constant infusion of ^{13}C-labeled octanoate to preterm infants reached a plateau within 1–3 h, thus indicating that the amount of MCT that can be oxidized by the liver is limited (29). Hence, MCFA not metabolized by the liver may be incorporated into VLDL-triacylglycerols by the liver, or they may remain in blood as nonesterified fatty acids. The higher concentration of non esterified fatty acids in the MCT group is almost completely explained by the higher 8:0 and 10:0 concentrations and as a consequence, the percentage distribution changes. Furthermore, MCFA present in plasma might have been released from adipose tissue, since infants fed MCT formulas may store up to 12% of 8:0 and 10:0 in adipose tissue (37).

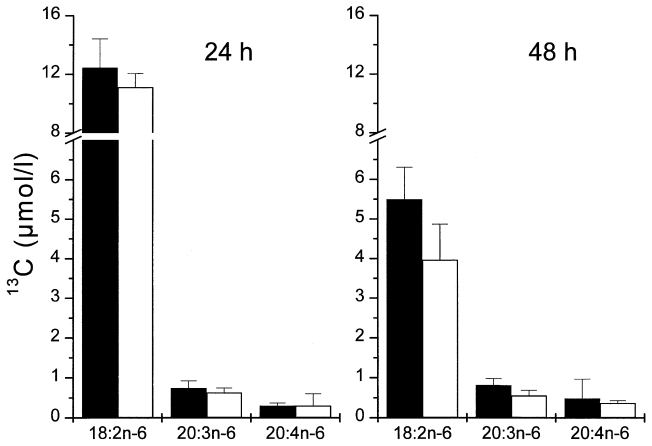

Fig. 2. ^{13}C-concentration (µmol ^{13}C/l, mean + SEM) in plasma phospholipid n-6 fatty acids in preterm infants fed control or MCT formulas 24 h and 48 h after tracer application (black columns, MCT group; white columns, control group), no significant differences between groups, but all values are significantly different from 0.

Concentrations of LCFA in plasma triacylglycerols of the two feeding groups were similar, although dietary intake of 16:0, 18:0, and 18:1 in the MCT group was almost 50% lower than in the control group (Table 1). Although triacylglycerols tend to reflect the dietary fatty acid pattern, no decrease in 16:0 was observed, and absolute amounts of other saturated fatty acids such as 14:0, 18:0, 20:0, 22:0, and 24:0 even increased. Absolute concentrations of 18:1n-9 in plasma triacylglycerols did not differ between groups, despite the low amount present in the MCT formula. Thus, the higher percentage of MCFA was largely compensated for by decreased 18:1n-9 percentages, as concentrations of polyunsaturated fatty acids also tended to be higher with the MCT diet. The high concentrations of saturated fatty acids and partly 18:1n-9 in the MCT group might have been caused by increased hepatic fatty acid synthesis either de novo, or by chain elongation, as suggested first in adults (8) and later in preterm infants with a high intake of MCT (38). Another factor explaining the increased plasma LCFA concentrations in MCT fed infants is the preferential oxidation of MCFA by the liver, which may preserve LCFA from oxidation (27). The observed concentration differences are in line with both explanations, as 18:1n-9 tends to be oxidized preferentially compared with palmitic acid (39). However, only reduced LCFA oxidation can explain the higher plasma concentrations of 18:2n-6 and 18:3n-3, which were fed in equal amounts with both diets. Furthermore, in triacylglycerols the MCT group presented higher concentrations of 20:2n-6, 22:4n-6, 22:5n-6, and 20:5n-3 than the control group ($P < 0.05$), which could also be due to reduced LCP oxidation.

Total triacylglycerol bound fatty acids were 28% higher in the MCT fed group than in the control group, although the difference was not statistically significant. This is in accordance with the reported 3-fold increase in fasting serum triacylglycerol concentrations (8) and enhanced secretion of VLDL by the liver (40) after MCT feeding.

In contrast to Carnielli et al. (9), we observed higher absolute and relative concentrations of 18:3n-3, 20:5n-3, 20:2n-6, and 22:5n-6 in plasma phospholipids of MCT fed infants, while we did not see lower values of 22:6n-3. The differences might be explained by the higher postnatal age of the infants or the shorter duration of intervention in our study. Compared with the influence of the MCT diet on triacylglycerols, the effects on plasma phospholipids are small. The concentrations of ^{13}C-labeled 18:2n-6 and its metabolites in phospholipids tended to be lower in the infants fed the MCT formula particularly at 48 h after tracer administration, although in this group tracer oxidation seemed to be lower. This corresponds to the larger pool size of polyunsaturated fatty acids in the MCT group (especially triacylglycerols) and thus more dilution of the tracer before incorporation into plasma phospholipids whose concentrations changed only marginally.

It has been shown that term and preterm infants are able to synthesize both 20:4n-6 and 22:6n-3 from their precursor fatty acids (21, 23). In the present study, determinations of ^{13}C excess in plasma phospholipid n-6 fatty acids allowed us to study 18:2n-6 metabolism in the two feeding groups. Since MCT feeding produces a slight hyperinsulinemic response (41, 42), it might enhance Δ5 and Δ6 desaturase activity (43). However, the ratios of ^{13}C enrichments and tracer concentrations of precursor and product fatty acids were similar between the feeding groups, indicating no influence of MCT on the fractional conversion of 18:2n-6 toward LCP.

Oxidation of all LCP (including 18:2n-6, 20:3n-6, and 20:4n-6) might have been reduced by MCT, similar to the effects on 18:2n-6 oxidation. No data on LCP oxidation in infants have been published, although experiments in animals have shown that dietary LCP are preferentially channeled into structural lipids (44) and are only oxidized to a limited extent (36). Nevertheless, preservation of LCP from oxidation might increase their concentrations in plasma lipids.

As MCT seems to decrease oxidation of 18:2n-6 and not to influence relative conversion rates, it might enhance absolute conversion of 18:2n-6 into LCP in situations when 18:2n-6 availability is limiting LCP synthesis. Although we did not measure ^{13}C excess in phospholipid n-3 fatty acids, the same hypothesis and approaches as for n-6 series would be valid to explain an influence of MCT on the concentration of n-3 polyunsaturated fatty acids, excluding a potential influence of high MCFA concentrations on peroxisomal chain shortening, which is required for 22:6n-3 synthesis (7)

In conclusion, our results show that feeding preterm infants with an infant formula providing 40% of total fatty acids as MCFA results in lower 18:2n-6 oxidation without affecting relative conversion of 18:2n-6 to longer chain metabolites. This spares essential fatty acids from oxidation.

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