Odd-Numbered Medium-Chain Triglycerides (Trinonanoin) in Total Parenteral Nutrition: Effects on Parameters of Fat Metabolism in Rabbits

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ABSTRACT. Odd-numbered medium-chain triglycerides (MCTs) might combine the advantages of "usual" MCTs applied in clinical nutrition with lower ketogenic action and the release of three carbon units. To test subacute toxicity, trinonanoin/long-chain triglyceride (LCT) (7/3 wt/wt) fat emulsions were given to rabbits (n = 8) for 11 days (7 h/d) within a total parenteral nutrition regimen at a dose of 46.5% of total daily energy. Comparisons were made with rabbits receiving equicaloric amounts of MCT/LCT (7/3, wt/wt) or pure LCT fat emulsions, as well as with orally fed controls. The trinonanoin/LCT emulsion was well tolerated by all animals. Body weight changes showed no statistically significant differences between groups. The enzymatic determination of triglycerides, nonesterified fatty acids, and free glycerol concentrations in plasma samples revealed similar results for both MCT groups. However, ketone body concentrations (3-hydroxybutyrate) were significantly lower after trinonanoin/LCT emulsion administration. In the trinonanoin/LCT group, the plasma concentrations of propionic acid as well as of other short-chain fatty acids continuously increased; on days 10 and 11, elevated amounts of propionic acid were also detected in the urine. The histologic examination of the gut mucosa revealed no distinct differences between groups. On the basis of the presented data, the trinonanoin/LCT emulsion showed no inferiority to "usual" MCT/LCT emulsions. The lower ketogenic effect as well as the marked increase in plasma short-chain fatty acid concentrations may encourage further testing of this substrate for total parenteral nutrition.

Medium-chain triglycerides (MCTs) given in combination with long-chain triglycerides (LCTs) have been shown to be favorable and safe substrates in total parenteral nutrition (TPN) of critically ill patients. In contrast to LCTs, their physical and biologic properties result in positive metabolic effects, but without adequate administration of glucose, MCTs are known to be ketogenic. As opposed to even-numbered fatty acids (FAs), during β-oxidation of odd-numbered FAs, propionyl residues should be released. Consequently, the lower production of acetyl coenzyme A (CoA) might result in reduced ketone body formation. Theoretically, assuming ceteris paribus conditions for the metabolism of even-numbered MCTs and odd-numbered MCTs (ONMCTs), ketone body formation from pelargonic acid would be expected to be at most two thirds that of even-numbered MCTs but might be still sufficient to obtain the benefits of ketones in the blood.

A more interesting aspect of ONMCTs in clinical nutrition is the possibility of propionic acid flux into the blood. If this concept were valid, a positive effect on the known TPN-induced atrophy of the gut mucosa could be expected. In TPN supplemented with the short-chain fatty acids (SCFAs) acetate, propionate, and butyrate, a significant reduction in mucosal atrophy has already been shown. At present, only one investigation has reported the short-term effects of pure ONMCT (trinonanoin [C₇TG]) emulsion infusion in dogs. Therefore, to investigate the metabolic consequences of C₇TG in TPN over a longer period of time. Because of the lack of knowledge on subacute toxicity of ONMCTs, a relatively high dosage was infused and parameters of fat metabolism were measured.

MATERIALS AND METHODS

Thirty male, sexually mature New Zealand bastard rabbits were randomly assigned to three TPN groups (n = 8 per group) and one control group (n = 6). The 24 rabbits in the TPN groups were catheterized (vena jugularis). All animals were fed the standard food Erka Z 6000 (R. Koch, Hamm, Germany) ad libitum for at least 2 weeks before the beginning of the study. At the start of the investigation, all rabbits were healthy judging by the evaluation of blood samples (concentrations of blood cells and hemoglobin, hematocrit, and pH value). The average body weight on day 1 after overnight fasting was 3.54 ± 0.37 kg.

The animals of the TPN groups received infusions of equicaloric amounts of fat within a TPN solution for 7 h/d over a total of 11 days (Table 1). The three groups were supplied with either C₇TG/LCT (7/3, wt/wt) emulsions, MCT/LCT (7/3, wt/wt) emulsions, or pure

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LCT emulsions. For each emulsion, egg yolk was used as an emulsifier (Table I). Of the daily infused amount of energy, 46.5% was provided by fat, 39.5% by glucose, and 14% by amino acids. The three complete diets differed minimally in energy density values (Table I). During the infusion time (7 h/d), the animals of the control group were offered isocaloric amounts of the standard food Erka Z 6000. The calculation of the total infusion volume and amount of standard food was done on the basis of the individual body weights on day 1 after overnight fasting. With the exception of the infusion period in the TPN-treated animals, all rabbits received water ad libitum. The TPN solutions were prepared daily by mixing the single nutrient preparations (as listed in Table I) in a laminar airflow bank (Köttermann, Ütte, Germany). The infusions were administered by means of Infusomat secura infusion pumps (B. Braun Melsungen AG, Melsungen, Germany).

All animals on 12 days of investigation, blood samples (each about 10 mL) were taken from the central ear artery after overnight fasting on days 1, 5, 9, and 12 as well as immediately before the 7-hour infusion/feeding period (7 h-i) on days 4, 8, and 11. In the plasma samples, the concentrations of 3-hydroxybutyrate (3OHB),\textsuperscript{12} acetocetate (AcAc),\textsuperscript{13} triglycerides (TGs), free glycerol (FG), and nonesterified FAs (NEFAs; Wako Chemicals GmbH, Neuss, Germany; No. 273-75409) were determined enzymatically. The given TG values (in millimoles per liter) were calculated from the total plasma content of glycerol after enzymatic hydrolysis of TG (Boehringer Mannheim GmbH, Mannheim, Germany, No. 701 912) and the plasma concentrations of FG (Boehringer Mannheim GmbH, No. 126 039). The method used for NEFA determination includes FAs with chain lengths as short as six carbon atoms. Plasma samples containing high substrate concentrations were diluted with NaCl solution (0.9% \#, Boehringer Mannheim GmbH).

Pooled urine was collected daily for each group. After semiquantitative testing for ketone body concentrations (Multistix 10SG, Bayer Diagnostik GmbH, Munich, Germany), the urine samples were stored at -28°C.

Plasma and urine samples were prepared for free SCFA determination according to the method of Björkman and Forslund\textsuperscript{14} and analyzed by gas chromatography (flame ionization detector), with isobutyric acid added as an internal standard. The glass column used (2 mm internal diameter, 6 mm external diameter, 3 m length) was filled with 5% FFAP on Chromosorb WHP, 80- to 100-mesh (Macherey-Nagel, Düren, Germany), and installed in an HP 5890A gas chromatograph (Hewlett-Packard, Taufkirchen, Germany). Acetic, propionic, butyric, valeric, isovaleric, caproic, and isocaproic acids were quantified by using commercially available standards of analytical grade (Sigma Chemie GmbH, Deisenhofen, Germany). After identification of the substances by retention times, quantification was made considering the "relative response factors."

On day 12, the animals were killed and parts of the gastrum, duodenum, ileum, cecum, and colon were prepared for the histologic examination at the Center for Pathology, Georg-August-Universität, Göttingen, Germany.

The results are given in terms of mean and standard error of the mean. Statistical analysis was performed with the program SPSS-PC+, version 3.1 (SPSS Inc., Chicago, IL). A three-factorial model was used, considering the factors type of triglyceride, day of blood sampling, and time of blood sampling. After analysis of variance, comparisons of means were made with the Student-Newman-Keuls test or the paired t test at an α level of 5%\textsuperscript{15}.\n
<table>
<thead>
<tr>
<th>Nutrient preparations*</th>
<th>Amount of nutrients (g)\textsuperscript{+}</th>
<th>Energy supply</th>
<th>Infusion volume (mL)\textsuperscript{+}</th>
<th>Energy density (kJ/mL)\textsuperscript{+}</th>
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<tbody>
<tr>
<td>Glucose (37.5% wt/wt)#†</td>
<td>9.00</td>
<td>142</td>
<td>240</td>
<td>7.80</td>
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<td>Amino acids (12.5% wt/wt)§</td>
<td>3.00</td>
<td>50</td>
<td>12</td>
<td>2.08</td>
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<td>Fat emulsions (20% wt/wt)#§</td>
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<td>167</td>
<td>40</td>
<td>19.7</td>
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<tr>
<td>C₄TG/LCT (7/3, wt/wt)#§</td>
<td>4.28</td>
<td>167</td>
<td>40</td>
<td>19.7</td>
</tr>
<tr>
<td>MCT#</td>
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<td></td>
<td>3.80</td>
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<td>LCT#</td>
<td></td>
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<td>3.80</td>
<td>167</td>
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<tr>
<td>Σ Energy#</td>
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<td>Emulsion of fat-soluble vitamins$§</td>
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<tr>
<td>Trace element solution$§</td>
<td></td>
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\textsuperscript{+}Per kg body weight per day; infusion period of 7 h/d.
\textsuperscript{†}Glucose 37.5% with electrolytes.
\textsuperscript{\#}Aminoplasma L, 12.5% without carbohydrates.
\textsuperscript{§}In 100 mL: 2.5 g glycerol; 1.2 g phospholipids from egg yolk as emulsifier.
\textsuperscript{\#}Emulsified together.
\textsuperscript{*}All preparations from B. Braun Melsungen AG, Melsungen, Germany.
\textsuperscript{\#}Commercially available MCT oil.
\textsuperscript{**}Endolipid.
RESULTS

The C₅TG/LCT fat emulsion was well tolerated by all rabbits. Until the end of the study, the average body weight of the rabbits in all groups decreased. With the exception of day 2, no significant differences existed in average body weight changes between groups. Mean caloric intake of the control animals was 25% beneath the provided amount.

As plotted in Figure 1, at the end of the daily infusion periods (days 4, 8, 11; 7 h⁻¹), no statistically significant differences in the mean TG, NEFA, or FG concentrations could be found between groups C₅TG/LCT and MCT/LCT (with the exception of FG on day 8). However, compared with the LCT group, mean TG, NEFA, and FG concentrations were significantly higher in both MCT groups. After overnight fasting on days 9 and 12, the FG concentrations in the C₅TG/LCT group were found to be significantly higher than the concentrations in the other TPN groups and the control group (Fig. 2); on day 12 (fasted), the C₅TG/LCT emulsion-treated group also had increased values for TGs and NEFAs.

The highest ketone body concentrations were measured in the MCT/LCT group at the end of the daily infusion period (Fig. 3). In comparison with the C₅TG/LCT group, the administration of MCT/LCT emulsions caused an approximately threefold increase in plasma 3-OHB concentrations on days 8 and 11 (7 h⁻¹); at the same time, the mean AcAc levels of both MCT groups were not significantly different but were higher than the level in the LCT group. Regarding the sum of ketone bodies, the differences between the LCT group and both MCT groups were statistically significant.

In none of the urine samples were ketone bodies detected.

As shown in Table II, at the end of the investigation period the plasma concentrations of all SCFAs were up to 20 times higher after C₅TG/LCT administration than after LCT or MCT/LCT infusion. Even in comparison with the control group, all values on day 12 (fasted) were significantly elevated after TPN with C₅TG/LCT emulsions. Compared with controls, the rabbits of the MCT/LCT and the LCT groups revealed lower concentrations of free acetic, propionic, and butyric acid at the end of the infusion and feeding period (day 11).

The changes in plasma SCFA concentrations in the C₅TG/LCT group in the course of the investigation were statistically significant for acetic, propionic, butyric, and valeric acid (Fig. 4). In the plasma samples taken at time point 7 h⁻¹, a steady increase in the concentrations of these acids could be noticed. Also, in fasted state, the mean values at the end of the study (day 12) were significantly higher compared with the preexperimental values (day 1).

The renal excretion of propionic acid at the beginning of the study was < 0.5 μmol · day⁻¹ · animal⁻¹ in all groups. On days 10 and 11 only in the C₅TG/LCT group, elevated amounts of propionic acid in the pooled urine were determined with values of 7.65 and 3.14 μmol · day⁻¹ · animal⁻¹, respectively. The concentrations of the other SCFAs detected in the urine of this group (acetic acid < 60, butyric acid < 0.8, isovaleric acid < 0.2, and valeric acid 3.5 μmol · day⁻¹ · animal⁻¹) showed no systematic changes by time.

The histologic examination of the gut mucosa revealed no clear differences between the TPN groups. In rabbits of all three TPN groups, a slight atrophy of the mucosal villi was observed in the ileum.

DISCUSSION

For initial studies on the tolerance of new fat emulsions, rabbits have proved to be a suitable and sensitive animal model. At a rather high administration dose (Table I), none of the animals in the TPN groups showed an apparent impairment in their general health. Far before reaching the range of acute toxicity, medium-chain FAs, including pelargonic acid (nonanoic acid), are known to cause functional changes in the
central nervous system, narcotic effects, and coma. For instance, somnolence was induced in dogs at plasma octanoic acid levels averaging 0.78 mmol/L and onset of coma occurred at plasma concentrations of 1.44 mmol/L (in dogs) up to 8 mmol/L (in rats). In the present study, the high plasma NEFA concentrations in animals of both MCT groups of up to 14 mmol/L (days 4, 8, 11; 7 h-i) should mainly reflect the FA composition of the infused fat emulsions, but no changes in behavior patterns of these rabbits could be noted.

Although the average body weight in each experimental group decreased, no significant differences in body weight changes between groups existed. Therefore, it is suggested that as an energy source the C,TG/LCT emulsion is comparable to the other tested fat emulsions within 11 days of TPN.

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**Table II**

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Day/time of blood sampling</th>
<th>C,TG/LCT</th>
<th>MCT/LCT</th>
<th>LCT</th>
<th>Control</th>
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<tbody>
<tr>
<td>Acetic acid</td>
<td>11/7 h-i</td>
<td>105.3 ± 5.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35.3 ± 5.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>29.3 ± 1.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>89.4 ± 2.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>12/fasted</td>
<td>142.2 ± 9.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.4 ± 1.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26.7 ± 1.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12.5 ± 0.2&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Propionic acid</td>
<td>11/7 h-i</td>
<td>23.7 ± 1.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.1 ± 0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.6 ± 0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.9 ± 0.5&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>12/fasted</td>
<td>11.8 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.4 ± 0.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.8 ± 0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.4 ± 0.2&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Butyric acid</td>
<td>11/7 h-i</td>
<td>4.1 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.8 ± 0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.9 ± 0.03&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11.7 ± 0.6&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>12/fasted</td>
<td>6.5 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.9 ± 0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.0 ± 0.03&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.6 ± 0.03&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Isovaleric acid</td>
<td>11/7 h-i</td>
<td>6.9 ± 0.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.1 ± 0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.4 ± 0.0&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td>12/fasted</td>
<td>4.8 ± 0.2&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>1.6 ± 0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.2 ± 0.1&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Valeric acid</td>
<td>11/7 h-i</td>
<td>6.6 ± 0.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ND&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td>12/fasted</td>
<td>6.7 ± 0.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ND&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ND&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ND&lt;sup&gt;b&lt;/sup&gt;</td>
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C,TG, trinomannin; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; ND, not detectable. Means within a time point and within fatty acid that have different superscripts (a, b, c) are significantly different at p ≤ .05 (Student-Newman-Keuls).
In the only investigation infusing pure C\textsubscript{5}TG (1 g · kg body weight\textsuperscript{-1} · day\textsuperscript{-1}) in dogs over 1 hour, no significant differences in the maximal plasma TG and NEFA concentrations were found compared with even-numbered MCT.\textsuperscript{10} The results of the present study confirm these findings (Fig. 1). So the velocity of TG hydrolysis and of cellular uptake of released FAs seems to be independent of an even or odd number of C-atoms in the FA molecule. Considering the 1.6-fold amount of TG moles infused in the MCT groups, the differences in the TG, NEFA, and FG concentrations between the MCT and LCT groups disappeared. Thus, as shown for MCT/LCT emulsions,\textsuperscript{22-26} the clearance of C\textsubscript{5}TG/LCT emulsions was faster than that of LCT emulsions, because in both MCT groups no accumulation of TGs, NEFAs, and FG was noted at the end of the daily infusion.

A hint for a slower elimination of C\textsubscript{5}TG from plasma was given by Guisard et al.,\textsuperscript{10} who found that after stopping the infusion the preexperimental values of TGs and NEFAs were reached later in comparison with even-numbered MCTs. Significantly higher TG and NEFA values on day 12 (fasted) and the elevated concentrations of FG after overnight fasting on days 9 and 12 may support the cited results.\textsuperscript{19} Another explanation for the higher fasting FG values after C\textsubscript{5}TG/LCT administration is the glucogenic potential of propionic acid. Depending on the metabolic state, propionic acid can act as substrate for gluconeogenesis by entering the tricarboxylic acid cycle via succinyl CoA, a precursor of oxaloacetate,\textsuperscript{27} and probably reveal a glycerol-sparing effect.

The postulated lower ketogenic action of ONMCTs as even-numbered MCTs (see introduction) was confirmed by the 3OHB concentrations in the plasma (Fig. 3). In the C\textsubscript{5}TG/LCT group, the sum of measured ketone bodies at time point 7 h\textsuperscript{-1} ranged between 49% (day 11) and 79% (day 4) of the means obtained in the MCT/LCT group. However, compared with the LCT group, blood ketone body concentrations after C\textsubscript{5}TG/LCT infusion were higher and similar to the concentrations measured in the control group after overnight fasting. Because it was shown that even small physiologic increases in blood 3OHB levels can save protein by reducing amino acid oxidation and enhancing protein synthesis,\textsuperscript{7} the ketone body concentrations in the C\textsubscript{5}TG/LCT group may be high enough to achieve this effect.

With similar AcAc levels in both MCT groups, significantly higher ratios of 3OHB concentration to AcAc concentration in the MCT/LCT group at time point 7 h\textsuperscript{-1} were calculated. The mean values of this ratio (days 4, 8, and 11; 7 h\textsuperscript{-1}) were in the range of 1.3 to 1.7 in the C\textsubscript{5}TG/LCT group and from 3.3 to 4.5 in the MCT/LCT group. This ratio should reflect the intramitochondrial redox status (nicotinamide adenine dinucleotide [reduced form]/nicotinamide adenine dinucleotide [oxidized form])\textsuperscript{28} and would therefore suggest a faster β-oxidation of even-numbered medium-chain FAs. In contrast, Guisard et al.\textsuperscript{10} calculated similar ratios for both groups.
The results show for the first time in mammals that \( \beta \)-oxidation of ONMCTs causes an increase in plasma propionic acid content as well as in renal propionic acid excretion. The liver, as the most important organ for the metabolism of even-numbered MCTs and probably also for ONMCTs, should be mainly responsible for the propionic acid release. In studies on the fate of propionic acid produced in the large intestine, the liver was shown to be by far the dominant organ for propionic acid uptake and metabolism. However, other tissues are also able to metabolize propionic acid. Assuming complete \( \beta \)-oxidation of pelargonic acid, from the amount of C5TG infused in the present study (Table I), 25 mmol \( \cdot \) kg body weight \(^{-1} \) \( \cdot \) day \(^{-1} \) propionyl CoA should be formed. This should have exceeded the capacity of the liver for utilization of propionic acid, resulting in increasing plasma concentrations. After overnight fasting, the plasma propionic acid contents were reduced (Table II), but neither preexperimental values (day 1, Fig. 4) nor the concentrations measured in the other groups (day 12, Table II) were reached. Therefore, it is suggested that the amount of C5TG/LCT emulsion infused was too high to avoid accumulation of propionic acid in the blood.

Surprisingly, propionic acid was not the only SCFA increasing during TPN with C5TG/LCT emulsions. A statistically significant increase in the plasma concentrations of acetic, butyric, and valeric acid could be seen as well (Fig. 4). Caproic acid and isocaproic acid were also detectable in the plasma samples on days 8 and 11 (7 h - 1), respectively. Different mechanisms may account for the increase of the plasma SCFA concentrations. First, high propionyl CoA concentrations have been shown to inhibit succinyl-CoA ligase, a key enzyme of the tricarboxylic acid cycle; an accumulation of acetyl CoA/acetyl carnitine may be the result. An increasing metabolism of propionic acid by minor pathways would also produce acetyl CoA. An existing concurrence of acetic and propionic acid for free CoA and carnitine may lead to a relative deficiency of these metabolites and free acids might be released into the blood. Second, during a possible impairment of the mitochondrial FA oxidation, peroxisomal \( \beta \)-oxidation of pelargonic acid may have been more important, producing FA "fragments" as well as free acetic acid. Third, acetyl CoA and propionyl CoA could have competed as substrates for enzymatic reactions, as shown in patients suffering from organic acidemias; reactions forming SCFAs can be hypothesized.

Butyrate has proved to be the preferred substrate for colonic epithelial cells, followed (within the group of SCFAs) by propionate and acetate. However, a mixture of SCFAs (acetate, propionate, and butyrate) injected in the colon revealed a stronger stimulatory effect on mucosal growth of the small intestine than intracolonic infusion of butyrate solutions alone. Therefore, in spite of altered relative proportions of the individual acids in the C5TG/LCT group because of higher propionic acid concentrations (Table II), favorable effects regarding the integrity of the gut mucosa were to be expected. In contrast, the histologic examination of the intestinal mucosa revealed no distinct differences between TPN groups. However, these findings are not disappointing considering special properties of the chosen animal species (e.g., coprophagy and large cecum) and the short period of increased SCFA levels in this investigation. Moreover, in a study demonstrating the trophic effect of intravenously administered SCFAs in rats, higher serum SCFA concentrations may have been reached. With missing differences in mucosal impairment between the MCT/LCT group and the other TPN groups, an influence of ketone bodies on the integrity of the gut mucosa could not be seen.

**REFERENCES**