Feeding behavior in neonates whose diet contained medium-chain triacylglycerols: short-term effects on thermoregulation and sleep

Frédéric Telliez, Véronique Bach, André Leke, Karen Chardon, and Jean-Pierre Libert

ABSTRACT

Background: Feeding formulas for premature infants often contain medium-chain triacylglycerols (MCTs). However, previous studies in animals and adults showed that MCTs may decrease food intake. Objectives: The objectives were to determine in hospitalized premature infants whether food intake is modified by dietary MCT supply and to assess the effects on thermoregulation and sleep, which are involved in the regulation of energy metabolism and in the optimal physiologic development of the neonates. Design: Food intake, body mass, and nutritional efficiency during 3 consecutive days were compared in 2 groups of neonates according to the fat composition of their feeding formula (MCT group: 37% MCT, 63% long-chain triacylglycerols (LCTs); LCT group: 100% LCT). On the third day, sleep and metabolic rate were recorded in the morning during an interval between meals. Results: Regardless of day, energy intake was greater in the MCT group than in the LCT group (difference: 67.3 kJ · kg⁻¹ · d⁻¹; P = 0.007). Metabolic rate (1.8 mL · min⁻¹ · kg⁻¹; P < 0.001), cheek skin temperature (0.31°C; P = 0.04), and total sleep time (52 min; P = 0.01) were also higher in the MCT group. Conclusion: The ratio of MCTs to LCTs in neonates’ feeding formulas can modify physiologic functions involved in energy-balance regulation. Am J Clin Nutr 2002;76:1091–95.

KEY WORDS Feeding behavior, medium-chain triacylglycerols, neonate, thermoregulation, sleep

INTRODUCTION

Milk formulas for premature infants (whose digestive function is immature) often contain medium-chain triacylglycerols (MCTs), ie, those containing saturated fatty acids with carbon chain lengths of 6–10 atoms, which confer nutritional characteristics that differ from those of long-chain triacylglycerols (LCTs) (1). Compared with LCTs, MCTs are more easily hydrolyzed, better absorbed (2), and more rapidly oxidized (3). As a consequence, MCTs are often referred to as a source of readily available energy for premature infants.

However, MCTs could well have adverse effects, especially on feeding behavior. Dietary MCTs decreased short-term food intake in chickens (4), rats (5), and adult humans (6, 7). This effect could be attributed to the fact that MCTs increase the plasma concentrations of cholecystokinin (CCK) (8), a satiety hormone (9). Thus, in neonates, the MCT content of the diet may modify daily energy intake with potential long-term adverse effects on growth. This hypothesis remains the subject of debate.

The type of nutrient could also interfere with thermoregulatory and sleep processes, both of which are implicated in energy-balance regulation. The thermic effect of diet is an important component of body temperature maintenance in premature infants (10, 11). The duration and structure of sleep are also altered by the quality and quantity of food ingested (12–16). Modifications in body temperature and sleep patterns could be of paramount importance in the maturation of neonates’ central nervous system (17).

The present study aimed to determine whether neonates’ food intake is modified by the dietary supply of MCT. Repercussions of the diet on thermic effect and sleep were also assessed.

SUBJECTS AND METHODS

Subjects and feeding

Seventeen healthy premature neonates, nursed in closed incubators in a hospital pediatric department, were enrolled in this study after their parents were informed of the protocol and had given written, informed consent. The protocol was approved by the Regional Ethics Committee of Picardie. Neonates with neurologic or cardiorespiratory problems or infections, or any combination of those conditions, were not included in the experiment.

Neonates were randomly assigned to 1 of 2 groups (Table 1). No significant differences were observed between the 2 groups with regard to general clinical variables. The neonates were fed with 2 commercially available formulas, currently used in the hospital’s pediatric department, spanning the highest and the lowest rates of MCT supply. The 2 formulas were isoenetic and isonitrogenous [293 kJ/100 mL energy content, 57.7% carbohydrate (by wt), 14.6% protein, 24.8% fat, and 2.9% mineral components] and differed only in their relative fat composition, ie, the ratio of MCT to LCT (Table 1). The MCT group was fed with a formula enriched with MCTs, containing 37% MCT and

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Fat Composition</th>
<th>Carbohydrate (g/L)</th>
<th>Protein (g/L)</th>
<th>Fat (g/L)</th>
<th>Calcium (mg/L)</th>
<th>Phosphorus (mg/L)</th>
<th>Energy (kJ/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCT</td>
<td>37% MCT, 63% LCT</td>
<td>14.6%</td>
<td>57.7%</td>
<td>24.8%</td>
<td>2000</td>
<td>800</td>
<td>293</td>
</tr>
<tr>
<td>LCT</td>
<td>100% LCT</td>
<td>14.6%</td>
<td>57.7%</td>
<td>24.8%</td>
<td>2000</td>
<td>800</td>
<td>293</td>
</tr>
</tbody>
</table>

1 From the Unité de Recherches sur l’Environnement Toxique Périnatal—Adaptations Physiologiques et Comportementales (EA 2088), Faculté de Médecine, Université de Picardie Jules Verne (FT, VB, KC, J-PL), and the Service de Néonatologie-Pédiatrie IL CHU-Amiens Nord (AL), Amiens, France.
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TABLE 1
Characteristics of subjects and clinical variables for the 2 study groups and nutritional characteristics of the study formulas

<table>
<thead>
<tr>
<th></th>
<th>MCT group</th>
<th>LCT group</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 10)</td>
<td>(n = 7)</td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td>34 ± 2</td>
<td>34 ± 3</td>
</tr>
<tr>
<td>(wks of amenorrhea)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postnatal age</td>
<td>22 ± 8</td>
<td>26 ± 13</td>
</tr>
<tr>
<td>(d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>2.1 ± 0.3</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>(kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formula composition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy content (kJ/100 mL)</td>
<td>293</td>
<td>293</td>
</tr>
<tr>
<td>Lipid composition (% of total lipid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCT</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>LCT</td>
<td>63</td>
<td>100</td>
</tr>
<tr>
<td>Percentage by weight of total fat (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:0 Caproate</td>
<td>0.4</td>
<td>trace</td>
</tr>
<tr>
<td>8:0 Caprylate</td>
<td>21.5</td>
<td>trace</td>
</tr>
<tr>
<td>10:0 Caprate</td>
<td>15.2</td>
<td>trace</td>
</tr>
<tr>
<td>12:0 Laurate</td>
<td>0.9</td>
<td>6.6</td>
</tr>
<tr>
<td>14:0 Myristate</td>
<td>0.6</td>
<td>6.9</td>
</tr>
<tr>
<td>16:0 Palmitate</td>
<td>10.9</td>
<td>27.4</td>
</tr>
<tr>
<td>18:0 Stearate</td>
<td>3.2</td>
<td>7.5</td>
</tr>
<tr>
<td>18:1 Oleate</td>
<td>28.9</td>
<td>28.7</td>
</tr>
<tr>
<td>Polysaturated fatty acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Σn-3</td>
<td>2.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Σn-6</td>
<td>15.2</td>
<td>11.7</td>
</tr>
<tr>
<td>Others or unidentified</td>
<td>0.2</td>
<td>7.1</td>
</tr>
</tbody>
</table>

63% LCT (% by wt of total fat). The fat supply for the LCT group was not enriched with MCTs. At the time of the study, no commercial formula used in the pediatric department contained >40% MCT; a 40% component of MCT seems to be the maximum at which an overload of the β-oxidation capacity in premature infants, and therefore the stimulation of the ω-oxidative pathway secretion of dicarboxylic acids, can be avoided. The current tendency is to reduce to 0% the amount of MCT in the feeding formulas for premature infants.

Each neonate was fed with the formula for the 5 d immediately before each experimental session. Feeding nursing care corresponded to the usual procedure and was not modified by the experiment. Each neonate was fed by bottle, with feeding episodes occurring every 3–4 h according to the neonate’s feeding demands, eg, awakening, body activity, and crying. Food was given until the neonate appeared to be satiated, ie, stopped sucking the bottle.

Experimental design

Each infant was studied over 3 consecutive days (day 1–day 3), during which time food intake, body weight, and nutritional efficiency (ie, the ratio of energy supply and body weight gain, calculated over a 24-h period measured from 0800 on day 1 to 0800 on day 3) were recorded. Each neonate was weighed with accurate scales (± 5 g; Sartorius, Palaiseau, France) each morning before feeding. Food intake was estimated from the quantity of milk ingested by the neonate at each feeding episode.

On the third day, sleep and metabolic rate (oxygen consumption, $\dot{V}O_2$) were recorded in the morning during an interval between meals, ie, from 1 h after a feeding and continuing until spontaneous awakening occurred. This procedure standardized the measurements with regard to the postprandial metabolic state. Gudinchet et al (18) reported that measurements made over a span of 2–3 h can be extrapolated to a 24-h span, because the CV of recordings is low (3.5–6.6%) during that span.

Throughout the study, the neonates were nursed at thermoneutrality (19) in a closed, convectively heated incubator (MP4; Médipréma, Chambray-les-Tours, France). Neonates wore only a small diaper and were lying in a supine position on a mattress. The air temperature of the nursery room was controlled and kept constant at 25 °C with a relative air humidity of 40%. During the experiments, the neonates were kept under optimal conditions with minimal opening of the incubator portholes and no blood sampling or diaper changing to ensure that their energy requirement was not increased by activity.

Measurements

Metabolic rate ($\dot{V}O_2$ in mL·min$^{-1}$·kg$^{-1}$) was measured by indirect calorimetry via an open circuit. Expired gases were collected from a transparent plastic canopy placed over the neonate (head and trunk), into which incubator air was drawn. The rate of outflow air (expired respiratory gases + air) was 4 L/min. The oxygen and carbon dioxide concentrations of the air leaving the canopy were continuously measured with the use of a mass spectrometer (MGA-1100; Marquette, Paris) calibrated at the start of each experiment with standard gases of known concentration. The $\dot{V}O_2$ was calculated from the difference in the oxygen concentration of the air entering the canopy and that of the air leaving the canopy. The canopy thus provides an environment that allows noninvasive measurements of gas exchanges without the use of a mask, which would induce discomfort.

Esophageal temperature ($T_e$) was measured with a thermistor probe [YSI 402 (accuracy ± 0.1 °C); Bioblock, Illkirch, France] introduced via the mouth and inserted to a distance of 10 cm from the lips. Skin temperature ($T_s$) was averaged from 2 local skin temperatures measured with thermocouples [K (accuracy ± 0.15 °C); Bioblock], one applied to the right cheek and the other to the righthand side of the abdominal region. Sensors were fixed to the skin surface with rubber tape and covered with aluminum to eliminate the effect of heat radiation reflected from the incubator walls.

The metabolic rate and body temperatures were measured at 10-s intervals throughout the experiment. Because of a technical problem, the abdominal skin temperature was not recorded for one neonate.

Sleep stages (active sleep, intermediate sleep, and quiet sleep) were scored for each 30-s period (20) on the basis of electrophysiologic recordings: electroencephalograms from the right and the left Rolando-occipital leads, electrocardiogram, and respiratory signals. Eye movements were monitored with the use of a mechanogram attached to an eyelid (21). Throughout the experiment, visual observation of the neonate’s behavior was made by the same experimenter.

Statistics

Two-factor analysis of variance for repeated measures using the $\epsilon$ correction of Geisser and Greenhouse (22) and t tests were carried out to test the effects of various amounts of MCT on food intake, nutritional efficiency, metabolic rate, body temperatures, and sleep. Values expressed as percentages have undergone arc sine transformation to stabilize the variance (23). $P < 0.05$ was
accepted as the level of significance. Indicative results (ie, non-significant, 0.05 < P < 0.10) are sometimes given when relevant.

RESULTS

Food intake and nutritional efficiency

No significant differences in digestive physiologic function (regurgitation, presence of residue in the stomach, diarrhea, or constipation) were observed between the groups. The daily energy intake as a function of the 3 consecutive days is shown in Figure 1. No significant interaction between time and type of feeding was observed. It is striking that, throughout the experiment, food intake was significantly higher in the MCT group than in the LCT group (by 67.3 kJ · kg⁻¹ · d⁻¹; P = 0.007). This accounted for 14–16% of the total energy supply. As shown in Figure 2, the difference in favor of the MCT group resulted from the ingestion of more milk (11.3 kJ · kg⁻¹ · d⁻¹; P = 0.01) at each feeding episode; the number of feeding episodes each day did not differ significantly (MCT group: 7.1 ± 0.3 episodes; LCT group: 7.4 ± 0.5 episodes).

Over the duration of the experiment, intergroup differences in body mass gain (MCT group: 16 ± 13 g/kg; LCT group: 15 ± 11 g/kg) and nutritional efficiency (MCT group: 0.033 ± 0.026 g/kJ; LCT group: 0.036 ± 0.027 g/kJ) were not significant.

The thermic effect of diet

On the third day of the experiment, oxygen consumption was significantly higher (P < 0.001; Figure 3) in the MCT group (7.0 ± 0.5 mL · min⁻¹ · kg⁻¹) than in the LCT group (5.2 ± 1.1 mL · min⁻¹ · kg⁻¹), whereas the incubator air temperature did not differ significantly between the 2 groups (MCT group: 33.29 ± 0.22 °C; LCT group: 33.25 ± 0.58 °C) and remained in the thermoneutral range defined by Sauer et al (19). The level of carbon dioxide production (VCO₂) was 7.1 ± 0.5 mL · min⁻¹ · kg⁻¹ in the MCT group and 5.4 ± 1.3 mL · min⁻¹ · kg⁻¹ in the LCT group. The respiratory quotient did not differ significantly between the groups (MCT group: 1.02 ± 0.22; LCT group: 1.02 ± 0.12).

Esophageal temperature tended to be higher in the MCT group (37.12 ± 0.26 °C) than in the LCT group (37.03 ± 0.24 °C), but the difference was not significant. The intergroup difference was indicative for overall mean skin temperature (MCT group: 36.88 ± 0.24 °C; LCT group: 36.66 ± 0.25 °C; P = 0.08), but this was due only to a significantly higher cheek skin temperature (0.31 °C, P = 0.04) in the MCT group.

Sleep

Total sleep time was significantly (P = 0.01) shorter in the LCT group (−52 min) than in the MCT group (Table 2) as a consequence of an earlier awakening. The time of the sleep onset, wakefulness after sleep onset, and the frequency of sleep stage changes were not modified by the regimen. No significant differences in sleep structure were observed.
Another possible explanation relates to the sensory vagal nervous system, which appears to be elicited by a CCK-based chemical signal. This observation contains LCT (65–75 cP) in mixed flavored drinks (7). Nevertheless, adult humans and animals, MCT increased the daily energy intake in comparison with LCT by increasing the average food intake per feeding episode. Various hypotheses, all relating to signals that alter food intake, such as chemical signals from the intestines, mechanical signals from the stomach, and sensory stimulation, can explain this observation.

MCT ingestion elicits the endogenous secretion of CCK in rats (8). Furuse et al (5) used a CCK-A receptor antagonist to show that the inhibitory effect of MCT on food intake in rat is related in part to the CCK satiety signal. In neonates, CCK is produced in response to breast-feeding (24, 25). Marchini and Linden (26) pointed out that CCK concentration is positively correlated with the volume of milk ingested, which suggests that CCK is a major satiety signal and thus is a factor in the regulation of food intake in breast-feeding newborns. On the contrary, Tornage et al (25) did not find any increase in plasma CCK concentrations in bottle-fed, premature infants 3–4 d after birth. They (27) also stressed that plasma CCK did increase after feeding via nasogastric tube but only in combination with kangaroo care (ie, skin-to-skin contact between the mother and the baby). Thus, these findings suggest that physical contact with the mother is a prerequisite for the stimulation of CCK secretion during food intake. This was never the case in the present study.

Feeding nursing care (eg, type of bottle, milk color, type of teat, noise level in the environment) was not significantly different for the 2 groups. This rules out possible bias due to visual, mechanical, or auditory stimulation, which could affect cortical control of feeding behavior. Finally, attention should be paid to preabsorption satiating factors such as smell and taste. When a difference of olfactory or taste sensory stimulation was observed, it favored a preference for LCT consumption in rats (28) and chickens (4, 29). Differences between the viscosity of MCT (25–30 cP) and of LCT (65–75 cP) induce a lower palatability in the MCT regimen than in the LCT regimen (30, 31). Nevertheless, adult humans seem unable to distinguish MCT from corn oil (which predominantly contains LCT) in mixed flavored drinks (7).

As reported above, the effect of MCT on food intake does not appear to be elicited by a CCK-based chemical signal. This observation cannot explain the greater energy intake by the MCT group. Another possible explanation relates to the sensory vagal nervous signals from stomach distension, which project via the solitary tract nucleus in the satiety center within the hypothalamus’s ventromedian nucleus. The type (liquid or solid), energy density, osmolality, and quality (type of carbohydrates and proteins) of the food were the same for each of the 2 groups, and those factors cannot be implicated in a modification of gastric emptying. However, other studies have shown that gastric emptying is more rapid with diets containing a high proportion [50% (32) and 94% (33)] of MCT as fat than with diets containing a low proportion of MCT [14% (32) and 6% (33)], but this difference probably resulted from better direct absorption in the stomach (34). Therefore, the slower emptying occurring with LCT could enhance the filling and the distension of the stomach, inducing satiety more rapidly, as suggested by the lower food intake observed in the LCT group than in the MCT group. Under our experimental conditions, the most plausible explanation of the present results relates to distension-related afferent sensory inputs into the satiety center.

**DISCUSSION**

**Food intake**

In the present study, in contrast with the findings reported for adult humans and animals, MCT increased the daily energy intake in comparison with LCT by increasing the average food intake per feeding episode. Various hypotheses, all relating to signals that alter food intake, such as chemical signals from the intestines, mechanical signals from the stomach, and sensory stimulation, can explain this observation.

**Sleep**

The reduction in total sleep time in the LCT group was mainly attributed to earlier awakening, and it could be considered an integral part of the behavioral component of a feeding episode. As suggested by Himms-Hagen (41), in a hypothesis of thermoregulation feeding in newborns, the interval between meals (ie, the duration of sleep before the next meal) depends in part on the amount of the preceding food intake and therefore on the thermic effect of the food. As a result, the lower food intake in the LCT group could be lead to a shortened intermeal interval, which would reduce sleep time. It would be interesting to test this assumption over a 24-h period to ascertain the consequences of feeding behavior on the sleeping-waking cycle in neonates.

**Summary**

In conclusion, the ratio of MCT to LCT in neonates’ feeding formulas can modify physiologic functions involved in energy-balance...
regulation. Food intake, energy expenditure, and sleep time were greater in an MCT-fed group than in an LCT-fed group. It is interesting to point out the physiologic consequences of 2 formulas currently used in neonates, which differ only in the type and characteristics of the lipids they supply. This finding could improve the physician’s criteria for choosing the formula according to the neonate’s requirements. For example, when the physician is confronted with an insatiable neonate, it is better to prescribe the LCT formula. In contrast, the MCT formula is better for premature infants who have difficulty in maintaining their body temperature.

We dedicate this study to Professor Bernard Risbourg, Head of the Department of Pediatrics II of the University Hospital of Amiens, who died recently. We thank Marie-Christine Godefroy, supervisor of the nursing staff of Pediatrics II (CHU Amiens), and wish to acknowledge the work of the nursing staff.

REFERENCES