

MINIREVIEW

MEDIUM CHAIN FATTY ACID METABOLISM AND ENERGY EXPENDITURE: OBESITY TREATMENT IMPLICATIONS

Andrea A. Papamandjaris, Diane E. MacDougall, and
Peter J.H. Jones

School of Dietetics and Human Nutrition, Faculty of Agricultural and
Environmental Sciences, McGill University, Macdonald Campus,
Ste-Anne-de-Bellevue, Quebec

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Summary

Fatty acids undergo different metabolic fates depending on their chain length and degree of saturation. The purpose of this review is to examine the metabolic handling of medium chain fatty acids (MCFA) with specific reference to intermediary metabolism and postprandial and total energy expenditure. The metabolic discrimination between varying fatty acids begins in the GI tract, with MCFA being absorbed more efficiently than long chain fatty acids (LCFA). Subsequently, MCFA are transported in the portal blood directly to the liver, unlike LCFA which are incorporated into chylomicrons and transported through lymph. These structure based differences continue through the processes of fat utilization; MCFA enter the mitochondria independently of the carnitine transport system and undergo preferential oxidation. Variations in ketogenic and lipogenic capacity also exist. Such metabolic discrimination is supported by data in animals and humans showing increases in postprandial energy expenditure after short term feeding with MCFA. In long term MCFA feeding in animals, weight accretion has been attenuated. These differences in metabolic handling of MCFA versus LCFA are considered with the conclusion that MCFA hold potential as weight loss agents.

Key Words: medium chain fatty acids, energy expenditure, metabolism, obesity

Medium chain fatty acids (MCFA) containing 8-12 carbons are saturated compared to long chain fatty acids (LCFA) which contain 14 or more carbon atoms and can possess one or more double bonds. These structural differences affect molecular size and water solubility and can lead to differentiation between MCFA and LCFA during processes of digestion, absorption, and transport (1). In addition, small chain length dependent differences in energy content of triglycerides and constituent fatty acids (FA) exist (2,3). There has been growing evidence that in addition to the fate of nutrients as directed by ATP requirements, chain length- and saturation-dependent differentiation in metabolic disposal of dietary fatty acids occurs, potentially directing ingested fat toward oxidation versus storage and thus influencing energy expenditure (2,4,5,6). Differences in MCFA versus LCFA energy content, uptake, and transport as well as efficiency of energy transformation may therefore impact on long term energy balance. Data suggest that such differences have implications in treatment strategies for obesity. Dietary fat substitution of MCT for LCT has been shown to influence energy balance and may therefore promote weight reduction (6,7). To address the question of the effect of MCFA on energy balance, the purpose of this review is to examine MCFA intermediary metabolism and the effect of MCFA administration on thermogenesis and total energy expenditure. The potential use of MCT as weight loss agents is also explored.

Digestion and Absorption of Medium Chain Triglycerides

Metabolic discrimination between MCT and LCT commences in the gut. The smaller molecular weight of MCT as compared to LCT facilitates the action of pancreatic lipase and therefore increases the rate of digestion of MCT (1). Consequently, MCT undergo faster and more complete hydrolysis to MCFA than LCT to LCFA (8,9,10) and MCFA are absorbed more quickly into the intestinal lumen (1,11). In addition, due to the longer chain length specificity of acyl-CoA synthetase, MCFA are not significantly incorporated into triglycerides and the subsequent chylomicrons as are LCFA, and therefore leave the intestine and enter the blood faster (1).

Internal Transport of Medium Chain Fatty Acids

Following digestion and absorption into the intestinal mucosa from the lumen, saturated LCFA are incorporated into chylomicrons and transferred to the circulation primarily via the thoracic duct, thereby initially bypassing the liver (Figure 1) (12,13,14). In contrast, higher concentrations of MCFA and unsaturated LCFA, bound to albumin, travel directly to the liver in the portal blood (3,15). For example, 49% of intraduodenally infused C10:0 was recovered from the rat mucosa in the portal blood system compared to 7.8%, 6.4%, and 10.6% recovery of C18:1, C18:2, and C20:4 respectively (16). These results are consistent with the findings of McDonald et al. (13) who observed that 72%, 58%, 41%, 28%, 58%, and 68% of C12:0, C14:0, C16:0, C18:0, C18:2, and C18:3 respectively, bypassed the lymphatic pathway when individually infused in the rat duodenum.

The correlation between increasing FA chain length and incorporation into chylomicrons is also seen in humans. Results of Swift et al (17) indicate that the mass of triglyceride transported in chylomicrons from a formula-fed LCT diet was approximately five times greater than that from a MCT diet. Chylomicron transport of triglycerides in the MCT diet, determined by chylomicron triglyceride concentration, was found to be increased slightly from day 1 to day 6 of feeding, although the reincorporation of MCFA as MCT in chylomicrons remained a quantitatively negligible pathway of MCFA metabolism. MCFA are therefore transported directly to the liver via the portal circulation unlike LCFA which are preferentially incorporated into chylomicrons as LCT and transported via lymph.

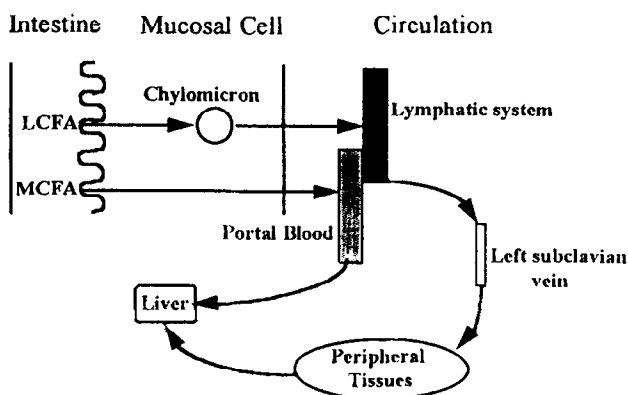


FIG. 1.

Differential MCFA and LCFA Transport. Following absorption from the intestine, MCFA pass directly from the mucosal cell into the portal vein and are transported to the liver attached to albumin. Conversely, LCFA are incorporated into chylomicrons which travel through the lymphatic system and exit at the left subclavian vein, circulating peripherally en route to the liver.

Oxidative Pathways of Medium Chain Fatty Acids

Once transported to the liver, MCFA may follow various catabolic pathways including beta-oxidation, omega-oxidation, and peroxisomal oxidation. Consequently, characteristic differences between MCFA and LCFA metabolism also exist following uptake by hepatic tissues. The fatty acyl synthetase responsible for TG re-esterification is most effective with FA of 14 or more carbons (18). As a result, few MCFA are recovered in triglyceride (19), phospholipid or cholesterol ester fractions (10) and low concentrations of MCFA are recovered in various tissues (20). The chain length preference of fatty acyl synthetase exists therefore as a major point of partitioning differentiation between MCFA and LCFA.

The majority of lipids are catabolized by mitochondrial beta-oxidation. LCFA or their acyl-CoA derivatives, once transformed into acylcarnitine by carnitine palmitoyl transferase (CPT) I, cross the mitochondrial membrane and are regenerated as long chain acyl-CoA in the mitochondrial matrix by CPT II (1); the concentration of LCFA crossing the membrane is therefore limited. Conversely, MCFA do not require a shuttle system to penetrate mitochondria (21). Mitochondrial acyl-CoA derived from either MCFA or LCFA then undergo oxidation with production of acetyl-CoA. Berry et al (22) noted that inhibition of FA entrance into the mitochondria caused a decrease in acetyl-CoA production, a decrease in CO₂ production derived from the acetyl CoA precursor, and a decrease in ketone production. Higher concentrations of acetyl-CoA were conducive to ketone body formation. Inhibition of CPT I more effectively reduced ketone body levels associated with LCT consumption compared to MCT consumption (21). Christensen et al (23) found that most C12:0 gained access to the mitochondria independently, however carnitine dependent mitochondrial oxidation may provide a minor pathway of C12:0 metabolism. Interestingly, Rossle et al (24) noted in healthy humans that a MCFA infusion depressed free carnitine levels and increased short chain acylcarnitine levels, relative to LCFA infusion. These results demonstrate the greater necessity of LCFA for a shuttle, CPT I and II, to enter the mitochondria for oxidation.

An alternate route for cystolic fat utilization is peroxisomal oxidation. At high concentrations of FA in the perfused rat liver, it is estimated that 25% of oxidation occurs in the peroxisome (25). Unlike

mitochondrial beta-oxidation, peroxisomal beta-oxidation produces H_2O_2 and is not coupled to a respiratory chain (26). Brady et al (27) found that the induction of peroxisomal and mitochondrial beta-oxidation was coordinated. Regardless of FA substrate, mitochondrial beta-oxidation exceeded (28) and preceded (29) that occurring in the peroxisome. The chain length specificity of acyl-CoA oxidase, an enzyme which may be rate limiting for peroxisomal oxidation, is dependent on acyl-CoA concentrations (1). Below 80 μM , palmitoyl-CoA showed the highest activity in rat liver extract; above that level, CoA derivatives of C8:0 and C12:0 produced the most activity, followed by C16:0 and C24:0 (30). Similarly, Handler et al (25) found that peroxisomes preferentially oxidized C12:0 in rat homogenates and perfused rat livers. This rate decreased with increasing and decreasing chain lengths (25,26). As peroxisomal beta-oxidation appears to be a significant pathway of fat catabolism and MCFA may have a high affinity for peroxisomal oxidation, this energetically inefficient pathway may contribute to enhanced thermogenesis.

Omega-oxidation of fat may also be structure specific. Omega-oxidation originates in the hepatocyte microsome, producing water soluble dicarboxylic acid which can be excreted in the urine. Christensen et al (19) found that C12:0 and C10:0 have the greatest affinity for omega-oxidation. Administration of MCT in children and animals has been associated with dicarboxylic aciduria (31,32,33), indicating a possible preference of MCFA for this oxidative pathway. Christensen et al (19) suggested that omega-hydroxy and dicarboxylic acids formed by FA omega-oxidation in the liver may be then further metabolized in the liver, accounting for acetate release from peroxisomes (34). Normal adults consuming a 3 day diet with MCT contributing 51% of energy, excreted less than 1% of the energy intake in the form of urinary dicarboxylic and keto acids (35). Thus, reduced energy accumulation associated with MCT ingestion does not appear to be the result of urinary excretion of omega oxidation products.

Ketogenesis and Lipogenesis of Medium Chain Fatty Acids

That MCT ingestion can result in increased ketogenesis in both animals and humans has been well documented (35,36,37). Several studies have indicated that MCT metabolism resulted in elevated B-hydroxybutyrate (B-OH) compared to LCT metabolism (4,24,38,39). However, other researchers have failed to notice similar effects of MCT metabolism (40,41).

Acetyl-CoA derived from MCFA and not directed toward ketone body formation or oxidation may be resynthesized into longer chain FA and esterified (7,10). Thus, LCFA may result from MCFA ingestion through de novo FA synthesis or through chain elongation. Christensen et al (23) noted that a significant amount of C12:0 was rapidly converted to C16:0 and lesser amounts of C14:0, C16:1, C18:0 and C18:1 in isolated hepatocytes derived from rats refed glucose.

Lipogenesis associated with LCT, MCT, and low fat (LF) consumption is frequently assessed by measurement of lipogenic enzyme activity in the liver and adipose tissue. In rat adipose tissue, the consumption of LCT was significantly more effective than MCT in inhibiting lipogenic enzyme activities (39,42). Chanez et al (40) found in rats that hepatic glucose-6-phosphate dehydrogenase, malic enzyme, ATP-citrate lyase, acetyl-CoA carboxylase and fatty acid synthase activities were 1.7, 2.6, 1.4, 1.5, and 1.4 fold higher on the MCT diet and 40%, 30%, 55%, 50%, and 45% lower on the LCT diet compared to the LF control diet, respectively. Geelen (43) observed that short-term exposure of isolated rat hepatocytes to MCFA stimulated fatty acid synthesis, as determined through increased hepatocellular carboxylase activity. Further to this, in vivo, Geelen et al (44) determined that in the rat model, a diet of MCT oil vs. corn oil increased hepatic acetyl-CoA carboxylase and fatty acid synthase. Foufelle et al (45) examined the effect of MCT consumption on lipogenic enzyme activity and gene expression during the suckling/weaning transition period in the rat. During

transition, lipogenic enzymes normally increase with the incorporation of a high carbohydrate rat chow diet. This effect fails to occur with weaning to a high fat diet, unless the diet contains MCT.

It has been suggested that these discordant lipogenic effects noted with MCT consumption may be due to carbohydrate content (36,40), polyunsaturated fat content (40,45) or the thyroid hormone response (36) to dietary nutrients. Consequently, all aspects of the diet must be considered for comparisons of dietary metabolic effects.

Macronutrient Balance and Medium Chain Fatty Acids

MCFA metabolism may be affected by the macronutrient composition of a mixed meal. Flatt et al (46) found no significant difference in postprandial oxidation following consumption of test meals containing similar amounts of carbohydrate and protein but differing across LCT, MCT or LF dietary treatments. The authors suggested that although the metabolism of carbohydrate and protein are highly regulated due to their limited storage ability, fat exhibits a greater degree of metabolic flexibility since it can either be oxidized or readily stored. Flatt et al (46) proposed that the metabolic pathway of dietary fat is not determined only by the composition or the amount of fat ingested; rather, fat metabolism proceeds in a manner which ensures that carbohydrate, protein, and energy balance are maintained. This theory is supported by Bennet et al (47) who added 50 g of dietary fat to a standard breakfast and did not see an increase in fat oxidation or energy expenditure during the following 24 h in humans. Schutz et al (48) observed a similar result when a fat supplement of 987 kcal/d did not alter 24 h energy expenditure and failed to promote the use of fat as a metabolic fuel. Conversely, other workers noted a significant negative correlation between carbohydrate intake and ^{13}C fatty acid oxidation rate to CO_2 (18) or fat intake and carbohydrate oxidation (49). Sato et al (50) found that total parenteral administration of an emulsion high in MCT resulted in increased glucose oxidation, compared to an emulsion high in LCT. Compared to prediet levels, subjects consuming 800 kcal/day diets required significantly more glucose to maintain euglycemia during continuous similar diets high in LCT (41). This result suggested MCT may stimulate insulin mediated carbohydrate metabolism.

Medium chain triglyceride metabolism may also be influenced by corresponding consumption of LCT. Johnson et al (20) found that the oxidation rate of ^{14}C MCT lipid emulsion was not significantly reduced when LCT were simultaneously administered, although there was a trend in this direction. Paust et al (18) observed that some patients oxidized C18:1 in a pure LCT emulsion more rapidly than in a mixed MCT/LCT emulsion. In other patients, no differences in the rate of FA oxidation were detected. Cotter et al (51) also identified competitive interaction between intravenous MCT and LCT emulsions in beagle dogs. These findings suggest that meal macronutrient composition must be taken into account if specific alterations of metabolism attributable to MCT are to be exploited.

Oxidation of Medium Chain Fatty Acids vs Other Fatty Acids

Structure dependent differences in oxidation of fat as a function of structure have been shown to occur using isotope tracer methodologies and respiratory gas exchange analysis. The utilization of [1- ^{14}C]octanoate has been shown to exceed [1- ^{14}C]oleate by at least five times in isolated hepatocytes incubated with corresponding fatty acid (52,53). Similar findings were noted in whole body fatty acid metabolism studies. Leyton et al (54), analyzing $^{14}\text{CO}_2$ evolution following oral dosing of various ^{14}C FAs to rats, reported that the oxidation decreased with increasing chain length. Faster oxidation resulted in lower retention of these LCFA in the carcass and liver. A similar result was reported where

lipid emulsions of ^{14}C MCT or ^{14}C LCT, when injected into rats, produced a more complete oxidation of MCT (90%) compared to the oxidation of LCT (45%) after 24 hours (20).

Fatty acid chain length seems to affect not only the quantity of fat oxidized, but the sequence in which oxidation takes place. In studies with normal children ranging from 3 months to 17 years who were administered ^{13}C -triolein, ^{13}C -palmitic acid or ^{13}C -trioctanoin, the appearance of $^{13}\text{CO}_2$ from ^{13}C -trioctanoin reached its maximum 2-4 hours after administration (55). ^{13}C -triolein oxidation peaked between 4-6 hours whereas labelled palmitic acid appeared as $^{13}\text{CO}_2$ more slowly, gradually increasing over a 6 h period. Cumulative excretion of $^{13}\text{CO}_2$ over 6 h was 27.6%, 11.3%, and 6.6% for trioctanoin, triolein, and palmitic acid respectively. Concurrent to these results, a single bolus intravenous infusion of ^{13}C -triolein or ^{13}C -trioctanoin in newborn infants was shown to produce peak $^{13}\text{CO}_2$ excretion levels 90 minutes and 45 minutes later respectively (18). Enrichment returned to baseline levels 10 hours after triolein and 8 hours after trioctanoin administration.

In human studies using respiratory gas exchange analysis, intravenous administration of MCT or LCT emulsions significantly increased the oxidation of MCFA over 10 hours, while the oxidation of LCFA remained similar to basal levels (56). Here, the concurrent rise in energy expenditure due to MCT administration could be entirely accounted for by energy expended for enhanced fat oxidation. White et al (57) saw an increase in post prandial energy expenditure on an MCT vs. LCT supplemented diet after 7 days of feeding, although the effect was attenuated after 14 days. Enhanced oxidation of MCT compared to LCT has also been shown to occur during exercise (58).

The method of administration of lipids for the purpose of determining FA oxidation may have a large bearing when comparing extent of oxidation. For example, the total oxidation of octanoate exceeds oleate in humans (59); this result is similar whether administered orally or parenterally to humans (59,60). In contrast, $^{13}\text{CO}_2$ breath enrichment of labelled oleate proceeds more rapidly when administered parenterally (59). Consequently, the length of feeding, the state of activity, and method of administration must be considered in examining effects of MCT administration on fat oxidation.

Thermogenesis and Medium Chain Fatty Acids

Increases occur in energy expenditure due to meal ingestion. This thermic effect of food (TEF) can be determined from respiratory gas exchange analysis by comparing whole body total energy expenditure (TEE) following consumption of a meal to resting metabolic rate (RMR). Flatt et al (46) compared the effect of ingesting an 858 kcal test meal containing 40 g MCT versus 40 g LCT over 9 hours. Energy expenditure due to the consumption of the test meal was similar and equivalent to 11.2% and 12.5% of energy contained in the LCT and MCT meals, respectively. Conversely, Scalfi et al (2) examined the TEF response to consumption of a 1300 kcal test meal containing 30 g of MCT or LCT in lean subjects. Total energy expenditure of subjects increased and the respiratory quotient decreased after the MCT test meal, resulting in a significantly elevated thermogenic response. Hill et al (7) examined energy balance during 7 days of overfeeding diets containing 40% MCT or LCT in healthy humans. Body weight, body composition and RMR did not change significantly during either diet treatment; however, following ingestion of 1000 kcal test meal containing MCT, TEF was significantly higher on both day 1 and day 6 compared to LCT. Seaton et al (4) compared the thermic effect of meals consisting almost entirely of 48 g of MCT or 45 g of corn oil. The MCT meal produced a significant increase in postprandial oxygen consumption compared to the LCT meal, thus resulting in an increased energy expenditure over basal level of 53 kcal and 17 kcal/h. These changes in energy expenditure were equivalent to 13% and 4% of energy contained in the MCT and LCT meals, respectively. Dulloo et al (6) saw a 5% increase in 24 h energy expenditure when humans were fed a diet containing 15-30 g MCT. Mascioli et al (56) noted that enhanced energy expenditure

associated with MCT ingestion occurred during intravenous administration of MCFA to hospitalized patients. A summary of the studies reflecting the positive effect of MCFA vs LCFA on postprandial energy expenditure can be found in Table 1.

Energy Balance and Medium Chain Fatty Acids

Long term energy balance studies have examined the effect of MCFA administration on energy balance, expressed as fluctuations in weight, fat deposition or energy deposition. In animals studies with rats ingesting diets containing 63% of metabolizable energy as MCT or LCT, Crozier et al (36) reported that the MCT treatment resulted in approximately 13% less energy intake and 30% less weight gain than did the LCT diet. These findings are in agreement with other animal studies conducted by Lavau and Hashim (42) and Geliebter et al (61) who observed reduced body weight and smaller fat depots during MCT feeding. Conversely, Wiley and Leveille (39) found that rats fed an MCT diet ad libitum did not gain less weight compared to rats on similar diets containing lard and corn oil, but body composition measurements were not made, so that an effect of MCT in reducing fat gain cannot be ruled out. Geliebter et al (61), however, stressed the importance of controlling energy intake and physical activity to allow cross comparison among studies. Overfeeding rats with an MCT diet (45% energy) via gastronomy tube for 6 wk reduced weight gain by 20% and fat deposition by 23% compared to a similar LCT diet (61). A more realistic level of fat consumption by rats (32% metabolizable energy) showed that energy retention resulting from LF and MCT diet treatments over 45 days was 26% less than that from a LCT diet (40). Similar long term studies in humans are less common, although Yost and Eckel (41) found that obese women consuming 800 kcal/d liquid diets containing 24% of energy as MCT or LCT for up to 12 weeks did not differ in either the rate or the amount of weight lost; however, body composition was not measured and therefore any changes in total body fat could not be assessed.

The effect of MCT and LCT on long term energy balance needs to be considered in the context of possible adaptation to the MCT diet. Crozier et al (36) examined progressive adaptation to extended MCT consumption in rats. Initially, elevated ketone body concentrations associated with consumption of high fat diets were noted, particularly with the MCT diet. Ketone body concentrations continually declined, and by day 44 were approximately 50% of the initial levels. In rats receiving 32% metabolizable energy as MCT or LCT compared to LF controls, Chanez et al (40) observed that plasma ketone body concentration was initially elevated with MCT consumption, but by day 45 this effect was no longer significant. This adaptive response may involve decreased ketone production and/or increased utilization.

In humans, Hill et al (7) found adaptive affects of MCT consumption to occur rapidly. Following ingestion of 1000 kcal meals containing LCT, TEF did not change significantly during a 6 day LCT feeding regime; TEF due to MCT feeding increased significantly over 6 days (7). Fasting TG levels, which were not different between diet treatments on day 1 were nearly 3 fold higher on day 6 of the MCT diet treatment versus the LCT diet treatment. Hill proposed that increased TEF on day 1 of the MCT diet may be due to increase ketone body formation. The additional rise in TEF by day 6 of the MCT diet may have been a result of a shift toward de novo fatty acid synthesis. This possible explanation is supported by Hill et al (38) who found that, relative to the LCT diet treatment, the composition of plasma TG on day 6 of the MCT diet contained twice as much C16:0; however, the C16:0 content of the MCT diet was 5 fold less than that contained in the LCT diet. Increases in C18:0 and C18:1 levels associated with the MCT diet treatment suggested that chain elongation and desaturation also occurred (38). White et al (57) observed an attenuation of the effect of MCT on postprandial energy expenditure after 2 weeks of feeding, offering evidence that adaptive effects may exist. This effect was also reported by MacDougall et al (62) who demonstrated that following an

TABLE 1

Summary of Studies Illustrating the Positive Effect of Medium Chain Versus Long Chain Triglyceride Consumption on Postprandial Thermogenesis in Humans

Subjects	Energy content (kcal)	Macronutrient composition	Treatment fat	Difference in TE _F [†] (medium vs long chain triglycerides)	Reference
7 lean males	400	100 % fat	48 g MCT oil vs 45 g corn oil	53 vs 17 kcal*	Seaton et al. 1986
10 lean males	1000	15 % protein 45 % carbohydrate 40 % fat	MCT oil vs LCT oil	day 1: 80±8 vs 58±8 kcal* day 6: 120±13 vs 66±10 kcal*	Hill et al. 1989
6 lean males	1300 LCT meal	15 % protein	30 g MCT oil vs	lean: 366.5±8.6 vs 246.8±29.6 kcal*	Scalfi et al. 1991
6 obese males	1270 MCT meal	55 % carbohydrate 30 % fat	30 g corn oil	obese: 367.1±52.4 vs 222.4±36.8 kcal*	
8 lean males	weight maintenance	15 % protein 45 % carbohydrate 40 % fat	30 g MCT oil per day/ 10 g per meal	9370±490 vs 8899±481 kJ*	Dulloo et al. 1996

Energy expenditure was measured for 6 hours with the exception of Dulloo et al. (6) where measurement was for 24 hours indicates significant difference ($p < 0.05$)

average of 8 and 11 days of feeding, no differences in postprandial energy expenditure existed between a breakfast rich in MCT versus LCT.

Results of human feeding studies challenge, therefore, current notions concerning classical metabolic pathways of ingested food as evidenced by differences in fat oxidation and TEF of MCFA and LCFA. It has been generally assumed that 5-10%, 0-3%, and 20-30% of energy contained in carbohydrate, fat and protein respectively will be expended during the process of thermogenesis (63). However, Hill et al (7) estimated that obligatory costs of octanoate oxidation were 3.3% if directed toward oxidation, compared to 6.7% if directed toward ketone formation and 32.3% if directed toward de novo FA synthesis. Thus, the obligatory thermogenic costs of MCFA ingestion may be in excess of traditional thermogenic costs of fat metabolism based on characteristic long chain metabolic pathways. This difference bears importance for studying MCT metabolism in man using indirect calorimetry; classical equations for calculating fat oxidation are based on values obtained using LCT, and may require modification for trials involving MCT feeding. With respect to weight control, this increase in thermogenesis may affect energy balance by increasing energy expenditure without altering energy intake and consequently may induce weight loss if energy intake is stabilized as expenditure increases.

Potential for Use of Medium Chain Triglycerides for Treatment in Obesity

The previous discussion illustrates the concept that the metabolism and the thermogenic effects of MCFA are different as compared to LCFA. The positive effect of MCFA on postprandial energy expenditure and fat oxidation has a potential application in body weight regulation. When an organism is in energy balance, the amount of energy entering the system equals that being expended. Schutz (64) proposes the model that if the amount of energy entering the system increases, the amount of energy expended will also increase as lean tissue mass grows to support the increase in fat tissue. The result is an elevation in body weight to a level at which a new equilibrium of energy expenditure and energy intake is achieved. This model expands upon the dynamic equilibrium hypothesis initially described by Payne and Dugdale (65). A corollary to this is that if the amount of energy expended increases and the amount of energy intake stays the same, the body compensates to reach a new energy equilibrium. This is accomplished by decreasing body weight until a new energy equilibrium is achieved. Such a scenario is represented in Figure 2. As presented, the source of this energy expenditure increase is MCT feeding as a substitute for LCT in diet.

The postulated increase in energy expenditure is supported by the research presented in Table 1. Differences in energy expenditure seen between MCT and LCT feeding may translate into weight loss. For example, Dulloo et al (6) fed 30 g MCT in addition to a maintenance diet consisting of approximately 15% of energy as protein, 40% as fat, and 45% as carbohydrate. The difference in energy expenditure over 24 h as a result of 30 g MCT versus 30 g LCT was 9370 ± 490 kJ compared to 8899 ± 481 , a difference of 471 kJ, or 113 kcal. This difference can be translated into the equivalent of approximately 12.6 g fat/day, or one pound of fat (0.45 kg) over approximately 36 days. A greater rate of loss due to increased dietary substitution of MCT for LCT above 30 g and/or continuing the dietary regimen over an extended period may be extremely clinically important in the treatment of obesity. The relevance of such an increase is supported by the fat balance theory of Swinburn and Ravussin (66) who state that the major influence on fat oxidation is energy expenditure, with negative energy balance promoting fat oxidation. Consequently, a negative energy balance created by MCT ingestion may promote fat oxidation and weight loss in the obese, recognizing that energy intake must be actively maintained at a constant level.

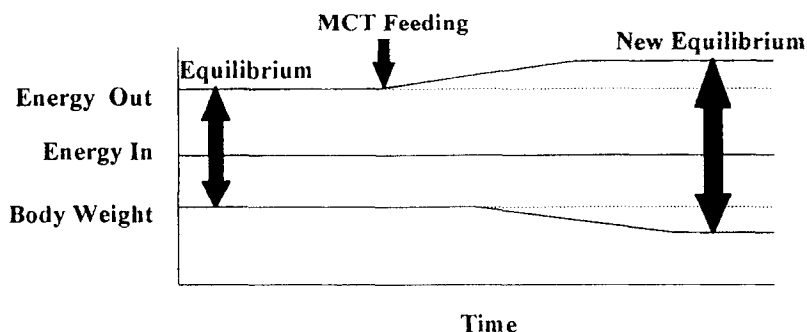


FIG. 2.

Energy Balance and Body Weight Before and After MCFA Feeding at Constant Energy Intake. At weight maintenance, energy intake equals energy expenditure. An increase in MCT ingestion at the expense of LCT disturbs the equilibrium by increasing the energy expenditure. To achieve a new equilibrium, body weight decreases.

In animal experiments, decreased weight gain during MCT feeding vs. LCT feeding has been observed by several researchers. Lasekan et al (67) demonstrated that rats receiving an intragastric or intravenous infusion over 24 h of a 3:1 emulsion of MCT and LCT vs. an LCT emulsion had one third the weight gain as well as a 13% increase in energy expenditure. During overfeeding for 6 weeks, Geliebter et al (61) observed that among rats fed 45% of calories either as MCT or LCT through a gastrostomy tube, the MCT-fed rats gained 20% less weight and possessed fat depots weighing 23% less than the LCT-fed rats. Similarly, Lavau and Hashim (42) saw a decrease in body weight and fat depots in rats fed a 55% by energy MCT diet as compared to a low fat diet, whereas a 55% LCT diet caused an increase in body weight and fat depots. Conversely, Dulloo and Girardier (68) saw no effect of carbon-chain length on energy expenditure or on energy partitioning during two weeks of calorie controlled refeeding in rats with 30% of energy as fat. However, in a subsequent isocaloric refeeding trial with fat as 50% of energy (69), MCT fed as coconut oil resulted in higher energy expenditure and less fat deposition as compared to LCT fed as lard. In general, these results suggest that MCT feeding is less weight promoting than LCT in rats.

In humans, there is a relative lack of studies examining the longer term effect of MCT feeding on weight gain and energy expenditure. Yost and Eckel (41) failed to see a difference in weight loss between two groups of obese women being fed hypocaloric diets over 12 weeks containing either 30% of calories as LCT or 24% as MCT and 6% as LCT; neither energy expenditure nor body composition was measured in this study. Hill et al (7) saw an increase in postprandial energy expenditure over 6 days of MCT vs LCT over feeding in healthy young men. In the longest MCT feeding trial to date that measured postprandial energy expenditure, White et al (57) saw an attenuation of the positive effect of MCT on energy expenditure after 14 days of MCT vs. LCT eucaloric feeding to non-obese college-age women. These findings suggest that the effect of increased energy expenditure may be transient.

In addition, the extent of lipogenesis that results after MCT feeding will have to be determined over the longer term. Hill et al (38) saw changes in triglycerides after 6 days of MCT vs. LCT feeding that were consistent with the hypothesis that MCT overfeeding may result in *de novo* lipogenesis and enhanced FA elongation by the liver. Potential lipogenesis as a result of MCT feeding is a concern as this effect may negate the positive effect of MCT on energy expenditure. However, whether significant lipogenesis will occur in eucaloric feeding remains to be determined.

The effect of MCT feeding on blood lipids also warrants further examination. In rats fed MCT vs. corn oil, MCT increased plasma triacylglycerols and decreased plasma cholesterol (44). Also in rats, Jones et al (70) observed an increase in both triglycerides and plasma total cholesterol following a coconut oil diet. In contrast, after 6 days of MCT vs. LCT feeding in humans, Hill et al (38) saw no effect of MCT feeding on plasma cholesterol, but there was a significant threefold increase in triglycerides. Cater et al (71) demonstrated that MCT oil, containing C8:0 and C10:0, had one-half the potency of palmitic acid in raising serum total and LDL-cholesterol concentrations. Resultant blood lipid profiles from MCT feeding need to be further elucidated to determine the potential of MCT as hypercholesteremic agents.

Conclusion

As presented, ample evidence exists that the pathways and energy costs of MCFA intermediary metabolism result in a characteristic enhancement of post prandial energy expenditure. Within a wide variety of circumstances, MCFA are consistently oxidized to a greater degree than LCFA. Ease of absorption, hepatic portal transport, carnitine independent mitochondrial metabolism and a low affinity for esterification may facilitate the rapid and greater oxidation of MCFA, thus making it a highly available energy substrate. Understanding the thermogenic effects of MCFA may provide valuable insight into the suitability of MCFA use in various clinical and therapeutic situations.

The capacity of MCFA use as an agent in the treatment of obesity is still to be determined. Eucaloric and hypocaloric mixed meal feeding paradigms that explore the long term effect of MCT on energy expenditure and blood lipid profiles are required to determine whether dietary substitution of MCFA for a proportion of LCFA can result in weight loss or in prevention of weight gain or regain following slimming. At a constant level of energy intake, increased dietary MCFA has the potential to be an effective tool in addressing the issue of obesity.

References

1. A.C. BACH and V.K. BABYAN. *Am J Clin Nutr* **36** 950-962 (1982).
2. L. SCALFI, A. COLTORTI, F. CONTALDO. *Am J Clin Nutr* **53** 1130-1133 (1991).
3. A.C. BACH, Y. INGENBLEEK, A. FREY. *J Lipid Res* **37** 708-726 (1996).
4. T.B. SEATON, S.L. WELLE, M.K. WARENKO, R. G. CAMPBELL. *Am J Clin Nutr* **44** 630-634 (1986).
5. J.O. HILL, J.C. PETERS, G.W. REED, D.G. SCHLUNDT, T. SHARP, H.L. GREENE. *Am J Clin Nutr* **54** 10-17 (1991).
6. A.G. DULLOO, M. FATHI, N. MENSI, L. GIRARDIER. *Eur J Clin Nutr* **50** 52-158 (1996).
7. J.O. HILL, J.C. PETERS, D. YANG, T. SHARP, M. KALER, N.N. ABUMRAD, H.L. GREENE. *Metabolism* **38** 641-648 (1989).
8. J. CLEMENT. *J Physiol* **72** 137-170 (1976).
9. G.J. FERNANDO-WARNAKULASURIYA, J.E. STAGGERS, S.C. FROST, M.A. WELLS. *J Lipid Res* **22** 668-674 (1981).
10. E.A. MASCIOLI, S. LOPES, S. RANDALL, K.A. PORTER, G. KATER, Y. HIRSCHBERG, V.K. BABAYAN, B.R. BISTRIAN, G.L. BLACKBURN. *Lipids* **24** 793-798 (1989).
11. W.F. CASPARY. *Am J Clin Nutr* **55S** 299S-308S (1992).
12. B. BLOOM, I.L. CHAIKOFF, W.O. REINHARDT, W.G. DAUBEN. *J Biol Chem* **189** 261-268 (1950).
13. G.B. MCDONALD, D.R. SAUNDERS, M. WEIDMAN, L. FISHER. *Am J Physiol* **239** G141-G150 (1980).
14. A. VALLOT, A. BERNARD, H. CARLIER. *Comp Biochem Physiol A* **82** 693-699 (1985).
15. B. BLOOM, I.L. CHAIKOFF, W.O. EINHARDT. *Am J Physiol* **166** 451-455.
16. A. BERNARD and H. CARLIER. *Exp Physiol* **76** 445-455 (1991).
17. L.L. SWIFT, J.O. HILL, J.C. PETERS, H.L. GREENE. *Am J Clin Nutr* **52** 834-836 (1990).

18. H. PAUST, T. KELES, W. PARK, G. KNOBLACH. *Stable isotopes in Paediatric Nutritional and Metabolic Research*. Chapman et al (Eds), 1-22, Intercept Ltd., Great Britain (1990).
19. E. CHRISTENSEN, M. GRONN, T.A. HAGVE, B.O. CHRISTOPHERSEN. *Biochim Biophys Acta* **1081** 167-173 (1991).
20. R.C. JOHNSON, S.K. YOUNG, R. COTTER, L. LIN, W.B. ROWE. *Am J Clin Nutr* **52** 502-508 (1990).
21. M.I. FRIEDMAN, I. RAMIREZ, C.R. BOWDEN, M.G. TORDOFF. *Am J Physiol* **258** R216-R221 (1990).
22. M.N. BERRY, D.G. CLARK, A.R. GRIVELL, P.G. WALLACE. *Eur J Biochem* **131** 205-214 (1983).
23. E. CHRISTENSEN, T.A. HAGVE, M. GRONN, B.O. CHRISTOPHERSEN. *Biochim Biophys Acta* **1004** 187-195 (1989).
24. C. ROSSLE, Y.A. CARPENTIER, M. RICHELLE, W. DAHLAN, N.P. D'ATTELIS, P. FURST, D.H. ELWYN. *Am J Physiol* **258** E944-E947 (1990).
25. J.A. HANDLER and R.G. THURMAN. *Eur J Biochem* **176** 477-484 (1988).
26. A.E. GANNING, M.J. OLSSON, E. PATERSON, G. DALLNER. *Pharmacol Toxicol* **1989** **65** 265-268 (1989).
27. P.S. BRADY, K.A. MARINE, L.J. BRADY, R.R. RAMSEY. *Biochem J* **260** 93-100 (1989).
28. F.A. REUBSAET, J.H. VEERKAMP, J.M. TRIJBELS, L.A. MONNENS. *Lipids* **24** 945-950 (1989).
29. R.K. BERGE, A. NILSSON, A.M. HUSOY. *Biochim Biophys Acta* **960** 417-426 (1988).
30. F.A. REUBSAET, J.H. VEERKAMP, S.G. BUKKENS, J. TRIJBELS, L.A. MONNENS. *Biochim Biophys Acta* **958** 434-442 (1988).
31. R.K. WHYTE, D. WHELAN, R. HILL, S. MCCLORRY. *Pediatr Res* **20** 122-125 (1986).
32. H. BOHLES, Z. AKCETIN, W. LEHNERT. *JPEN J Parenter Enteral Nutr* **11** 46-48 (1987).
33. K.Y. TSENG, R.L. GRIFFIN, D.S. KERR. *Metabolism* **45** 162-167 (1996).
34. F. LEIGHTON, S. BERGSETH, T. RORTVEIT, E.N. CHRISTIANSEN, J. BREMER. *J Biol Chem* **264** 10347-10350 (1989).
35. V.C. DIAS, E. FUNG, F.F. SNYDER, R.J. CARTER, H.G. PARSONS. *Metabolism* **39** 887-891 (1990).
36. G. CROZIER, B. BOIS-JOYEUX, M. CHANEZ, J. GIRARD, J. PERET. *Metabolism* **36** 807-814 (1987).
37. A. BACH, T. PHAN, P. METAIS. *Horm Metab Res* **8** 375-379 (1976).
38. J.O. HILL, J.C. PETERS, L.L. SWIFT, D. YANG, T. SHARP, N. ABUMRAD, H.L. GREENE. *J Lipid Res* **31** 407-416 (1990).
39. J.H. WILEY and G.A. LEVEILLE. *J Nutr* **103** 829-835 (1973).
40. M. CHANEZ, B. BOIS-JOYEUX, M.J. ARNAUD, J. PERET. *J Nutr* **121** 585-594 (1991).
41. T.J. YOST and R.H. ECKEL. *Am J Clin Nutr* **49** 326-330 (1989).
42. M.M. LAVAU, and S.A. HASHIM. *J Nutr* **108** 613-620 (1978).
43. M.J. GEELLEN. *Biochemical J* **302** 141-146 (1994).
44. M.J. GEELLEN, W.J. SCHOOTS, C. BIJLEVELD, A.C. BEYNEN. *J Nutr* **125** 2449-2456 (1995).
45. F. FOUFELLE, D. PERDEREAU, B. GOUHOT, P. FERRE, J. GIRARD. *Eur J Biochem* **208** 381-387 (1992).
46. J.P. FLATT, E. RAVUSSIN, K.J. ACHESON, E. JEQUIER. *J Clin Invest* **76** 1019-1024 (1985).
47. C. BENNETT, G.W. REED, J.C. PETERS, N.N. ABUMRAD. *Am J Clin Nutr* **55** 1071-1077 (1992).
48. Y. SCHUTZ, J. P. FLATT, E. JEQUIER. *Am J Clin Nutr* **50** 307-314 (1989).
49. K.J. ACHESON, A. THELIN, E. RAVUSSIN, M.J. ARNAUD, E. JEQUIER. *Am J Clin Nutr* **41** 881-890 (1985).
50. N. SATO, Y. MATSUBARA, K. YOSHIKAWA, T. MUTO. *JPEN J Parenter Enteral Nutr* **16** 451-454 (1992).
51. R. COTTER, R.C. JOHNSON, S.K. YOUNG, L.I. LIN, W.B. ROWE. *Am J Clin Nutr* **50** 794-800 (1989).
52. J.P. PEGORIER, P.H. DUEE, C. HERBIN, P.Y. LAULAN, C. BALDE, J. PERET, J. GIRARD. *Biochem J* **249** 801-806 (1988).
53. G.L. CROZIER. *J Nutr* **118** 297-304 (1988).
54. J. LEYTON, P. J. DRURY, M. A. CRAWFORD. *Br J Nutr* **57** 383-393 (1987).
55. J.B. WATKINS, P.D. KLEIN, D.A. SCHOELLER, B.S. KIRSCHNER, R. PARK, J.A. PERMAN. *Gastroenterology* **82** 911-917 (1982).
56. E.A. MASCIOLI, S. RANDALL, K.A. PORTER, G. KATER, S. LOPES, V.K. BABAYAN, G.L. BLACKBURN, B.R. BISTRAN. *JPEN J Parenter Enteral Nutr* **15** 27-31 (1991).
57. M.D. WHITE, A.A. PAPAMANDJARIS, P.J. JONES. *Obesity Res* **4S** 17S (1996).

58. P. SATABIN, P. PORTERO, G. DEFER, J. BRICOUT, C.Y. GUEZENNEC. *Med Sci Sports Exerc* **19** 218-223 (1987).
59. C.C. METGES and G. WOLFRAM. *J Nutr* **121** 31-36 (1991).
60. A.D. SCHWABE, L.R. BENNETT, L.P. BOWMAN. *J App Physiol* **19** 335-337 (1964).
61. A. GELIEBTER, N. TORBAY, E. F. BRACCO, S. A. HASHIM, T. B. VAN ITALLIE. *Am J Clin Nutr* **37** 1-4 (1983).
62. D.E. MACDOUGALL, P.J. JONES, J. VOGT, P.T. PHANG, D.D. KITTS. *Eur J Clin Nutr* **26** 755-762 (1996).
63. J.P. FLATT. *Recent Advances in Obesity Research. II*. G.S. Bray (Ed), 221-228, Newman, London (1978).
64. Y. SCHUTZ. *Metabolism* **44(S)** 7-11 (1995).
65. P. R. PAYNE and A. E. DUGDALE. *Lancet* **1** 583-586 (1977).
66. B. SWINBURN and E. RAVUSSIN. *Am J Clin Nutr* **57** 766S-770S (1993).
67. J.B. LASEKAN, J. RIVERA, M.D. HIRVONEN, R.E. KEESEY, D.M. NEY. *J Nutr* **122** 1488-1492 (1992).
68. A.G. DULLOO and L. GIRARDIER. *Metabolism* **41** 1336-1342 (1992).
69. A.G. DULLOO, N. MENSI, J. SEDOUX, L. GIRARDIER. *Metabolism* **44** 273-279 (1995).
70. P.J. JONES, J.E. RIDGEN, A.P. BENSON. *Lipids* **25** 815-820 (1990).
71. N.B. CATER, H.J. HELLER, M.A. DENKE. *Am J Clin Nutr* **65** 41-45 (1997).