Pharmacological Research 61 (2010) 208–212

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Medium-chain fatty acids: Functional lipids for the prevention and treatment of the metabolic syndrome

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ARTICLE INFO

Article history:
Received 29 September 2009
Received in revised form
15 November 2009
Accepted 15 November 2009

Keywords:
Metabolic syndrome
Obesity
Lipid metabolism
Type 2 diabetes
Medium-chain fatty acid
Medium-chain triglyceride

ABSTRACT

Metabolic syndrome is a cluster of metabolic disorders, such as abdominal obesity, dyslipidemia, hypertension and impaired fasting glucose, that contribute to increased cardiovascular morbidity and mortality. Although the pathogenesis of metabolic syndrome is complicated and the precise mechanisms have not been elucidated, dietary lipids have been recognized as contributory factors in the development and the prevention of cardiovascular risk clustering. This review explores the physiological functions and molecular actions of medium-chain fatty acids (MCFAs) and medium-chain triglycerides (MCTs) in the development of metabolic syndrome. Experimental studies demonstrate that dietary MCFAs/MCTs suppress fat deposition through enhanced thermogenesis and fat oxidation in animal and human subjects. Additionally, several reports suggest that MCFAs/MCTs offer the therapeutic advantage of preserving insulin sensitivity in animal models and patients with type 2 diabetes.

Contents

1. Introduction

Lifestyle-related diseases, such as obesity, hyperlipidemia, atherosclerosis, type 2 diabetes and hypertension, are widespread and increasingly prevalent in industrialized countries. Accompanied by the rapid increase in the number of elderly people, this becomes a medical and a socioeconomic issue. A clustering of metabolic disorders (in particular, abdominal obesity, hypertriglyceridemia, a low level of high-density-lipoprotein (HDL) cholesterol, hypertension and a high fasting-glucose level) in an individual, defined as metabolic syndrome, is known to increase cardiovascular morbidity and mortality [1]. According to the International Diabetes Federation, a person is defined as having metabolic syndrome if they have central obesity (waist circumference ≥94 cm for Europid men and ≥80 cm for Europid women) plus any two of the following four factors: raised triacylglycerol level (≥150 mg/dL, or receiving specific treatment for this lipid abnormality); reduced HDL-cholesterol (<80 mg/dL in males and <50 mg/dL in females, or receiving specific treatment for this lipid abnormality); raised blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg, or receiving treatment for previously diagnosed hypertension); and raised fasting plasma glucose (≥100 mg/dL, or previously diagnosed type 2 diabetes) [2]. It is estimated that around a quarter of the world's adult population have metabolic syndrome [2–4]. Subjects with metabolic syndrome have a threefold higher risk of developing coronary heart attack or stroke, and a twofold higher cardiovascular mortality than those without the syndrome [5].

Although the pathogenesis of metabolic syndrome is complicated and precise details of the underlying mechanisms are still unknown, it has been suggested that the quality of dietary lipids may be an important modulator of the risks associated with this syndrome [6,7]. In particular, animal studies and clinical trials have revealed different effects of individual fatty acids. Medium-chain fatty acid (MCFA) refers to a mixture of fatty acids which gen-

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doi:10.1016/j.phrs.2009.11.007

Table 1
Physiological effects of dietary MCFAs/MCTs in clinical studies.

Sample	Dose (period)	Subject	Effect	Reference
MCT	48 g Single administration	Healthy men (n = 7)	vs corn oil: a greater rise in postprandial oxygen consumption from the basal level	Seaton et al. [14]
MCT	40% 1 week	Healthy men (n = 10)	vs corn oil: a greater increase in energy expenditure	Hill et al. [15]
MCT	30 g Single administration	Lean men (n = 6) Obese men (n = 6)	vs corn oil: a greater postprandial thermogenesis in both lean and obese subjects	Scalfi et al. [16]
MCT	5–30 g Single administration	Healthy men (n = 8)	vs LCT: increased energy expenditure with low-to-moderate (15–30 g) MCT intake	Dulloo et al. [17]
MCT	15 g Single administration	Normal women (n = 8) Obese women (n = 8)	vs LCT: higher total lipid oxidation in both normal and obese subjects	Binnert et al. [18]
MCT	40% of energy as fat (80% of dietary fat as MCT) 2 weeks	Healthy women (n = 12)	vs beef tallow: increased endogenous long-chain saturated fat oxidation	Papamandjaris et al. [19]
MCT	67% of treatment fat 27 days	Obese women (n = 17)	vs beef tallow: increased energy expenditure and fat oxidation	St-Onge et al. [20]
MCT	64.7% 28 days	Overweight men (n = 24)	vs olive oil: increased energy expenditure and decreased adiposity	St-Onge et al. [21]
MCT	Two thirds of 75% added fat 28 days	Overweight men (n = 19)	vs olive oil: increased energy expenditure and fat oxidation	St-Onge and Jones [22]
MCT	10 g 12 weeks	Healthy men and women MCT (n = 41), LCT (n = 37)	vs blended rapeseed oil and soybean oil: decreased body fat accumulation in subjects with BMI $\geq$ 23 kg/m^2	Tsuji et al. [23]
MCT	5 g 12 weeks	Healthy men (n = 55) Healthy women (n = 18)	vs blended rapeseed oil and soybean oil: decreased body fat weights	Nosaka et al. [24]
MCT	5–10 g Single administration	Healthy men (n = 8) Healthy women (n = 8)	vs blended rapeseed oil and soybean oil: greater diet-induced thermogenesis	Kasai et al. [25]
MCT	18–24 g 16 weeks	Overweight men (n = 3) Overweight women (n = 28)	vs olive oil: lower endpoint body weight and fat mass	St-Onge et al. [26]
MCT	6 g 2 weeks	Recreational athletes (1 man and 7 women)	vs LCT: lowered blood lactate and RPE during MIE, extended duration of subsequent HIE	Nosaka et al. [28]
MLCT	14 g (1.7 g MCFAs) 12 weeks	Healthy human MCLT (36 men and 4 women) LCT (39 men and 3 women)	vs blended rapeseed oil and soybean oil: decreased body weight and body fat Lowered serum cholesterol level	Kasai et al. [34]
MLCT	20 g 12 weeks	Healthy male MCLT (n = 7), LCT (n = 6)	vs soybean oil: lowered rate of variation of body fat %	Matsuo et al. [35]
MLCT	20 g 3 weeks	College athletes (male, n = 6)	vs soybean oil: lowered rate of variation of serum TG Lowered rate of variation of body fat mass	Takeuchi et al. [36]
MLCT	25–30 g (3.25–3.9 g MCFAs) 8 weeks	Hypertriglyceridemic Subjects (MLCT, n = 51; LCT, n = 50)	vs LCT: greater decreases in BW, BMI, WC, body fat Lowered serum TG	Xue et al. [37]
MLCT	25–30 g (3.25–3.9 g MCFAs) 8 weeks	Hypertriglyceridemic Subjects (MLCT, n = 51; LCT, n = 50)	vs LCT: (in subjects age under 60 years) greater decreases in BW, BMI, WC, HC, WHR, body fat, TG, LDL-C, apolipoproteins Lowered ApoB, ApoA2, ApoC2 and ApoC3	Xue et al. [38]
MLCT	1680 kJ (39 kJ/g) Single administration	Healthy women (n = 15)	vs soybean oil: higher PTEE and greater thermic effects	Matsuo et al. [39]
MLCT	14 g Single administration	Healthy subjects (9 male and 11 female)	vs canola oil: a greater increase in DIT	Ogawa et al. [40]
FctO	40% of energy as fat (19.5% of energy as MCT oil) 4 weeks	Overweight men (n = 24)	vs olive oil: lowered endpoint TC and LDL-C Greater LDL particle size	St-Onge et al. [43]
FctO	40% of energy as fat (MCT oil, 50% of fat) 27 days	Overweight women (n = 17)	vs beef tallow: lowered TC and LDL-C Higher ratios of HDL:LDL and HDL:total cholesterol	Bourque et al. [44]
MCT	40% fat diet (77.5% of the fat Calories as MCT) 4 days	NIDDM patients (n = 10) non-diabetic subjects (n = 10, 4 hypertriglyceridemic, 6 normotriglyceridemic)	vs house hold shortning: increased insulin-mediated glucose metabolism in both diabetic and non-diabetic subjects	Eckel et al. [52]
MCT	18 g 90 days	Type 2 diabetic patients MCT (n = 20), LCT (n = 20)	vs corn oil: reduced body weight, WC, and HOMA-IR	Han et al. [53]
MCT	40 g divided to three times at 25-min intervals	Intensively treated type 1 diabetic patients (n = 11, 5 men, 6 women)	vs sucralose: reversed imapaired cognitive performance	Page et al. [54]

Apo, apolipoprotein; BMI, body mass index; BW, body weight; DIT, diet-induced thermogenesis; FctO, functional oil; HC, hip circumference; HDL, high-density-lipoprotein; HIT, high-intensity exercise; HOMA-IR, homeostasis model assessment of insulin resistance; LCSFA, long-chain saturated fatty acid; LCT, long-chain triacylglycerol; LDL-C, low-density-lipoprotein choleseterol; MCT, medium-chain triacylglycerol; MIT, moderate-intensity exercise; MLCT, medium- and long-chain triacylglycerol; NIDDM, non-insulin-dependent diabetes mellitus, PTEE, post-ingestive total energy expenditure; RPE, rating of perceived exertion; TC, total cholesterol; TG, triglycerid; WC, waist circumference; WHR, waist–hip ratio.

erally consist of 6–10 carbones. The names of MCFAs in edible oils and foods are caproic acid (hexanoic acid, C6:0), caprylic acid (octanoic acid, C8:0) and capric acid (decanoic acid, C10:0). MCFAs are present at about 15%, 7.9%, 6.8%, 6.9%, 6.6% and 7.3% (of total fatty acid) in coconut oil, palm kernel oil, butter, milk, yogurt and cheese, respectively [8,9]. Medium-chain triglycerides (MCTs) are MCFA esters of glycerol, and edible MCT-oils are obtained through lipid fractionation from edible fats (such as coconut oil and milk). Commercial MCT products are predominantly comprised of C8:0 and C10:0 in worldwide [9,10]. Since the 1950s, MCTs have been used for the dietary treatment of malabsorption syndrome because of its metabolic properties. MCTs are hydrolyzed rapidly and the resulting MCFAs are absorbed directly to the liver via the portal vein and are used as an energy source without using the carnitine transport system for mitochondrial entry [9–11]. Here, the effects of MCFAs/MCTs on metabolic syndrome in animal and clinical studies are reviewed, and Table 1 summarizes the physiological functions of MCFAs/MCTs shown in clinical studies.

2. Physiological effects of MCFAs on obesity and lipid metabolism

A physiological function of dietary MCTs in influencing body composition, compared with the effect of long-chain triacylglycerols (LCTs), has been reported. The consumption of MCTs diminished fat deposition through the enhancement of thermogenesis in rats [10–12]. Similarly, in clinical studies, fat oxidation and/or postprandial energy expenditure were greater after consumption of MCTs than after consumption of LCTs in both normal and obese subjects [13–22]. For example, Seaton et al. showed that MCT consumption (48 g) resulted in a greater rise in postprandial oxygen consumption from the basal level than did LCT consumption in healthy men [14]. Similar results were reported by Scalfi et al., showing that an MCT meal (30 g) induced greater postprandial energy expenditure than an LCT meal in both lean and obese subjects [16]. These effects have been observed even in studies with a low-dose supplementation of MCTs [23–26]. For example, Tsuji et al. reported that consumption of MCT at 10 g/day for 12 weeks reduced body weight and fat in subjects with BMI $\geq$23 kg/m^2 [23]. Nosaka et al. observed that daily consumption of test margarine containing 5 g of MCT for 12 weeks causes a greater decrease in body fat than that induced by LCT in healthy men and women [24]. Kasai et al. observed that 5–10 g of MCTs causes more diet-induced thermogenesis than that induced by LCT in healthy humans [25]. Recently, St-Onge and Bosarge reported that consumption of MCTs in the amount of 18–24 g/day as part of a weight-loss program for 16 weeks resulted in lowered endpoint body weight and fat mass compared with olive oil consumption in overweight men and women [26]. These results suggest the possibility that the substitution of MCTs for cooking oil or margarine could be useful for controlling body weight and fat in healthy subjects. Recently, the effects of a combination of a diet containing MCT and exercise on reduction of fat mass have been evaluated in rats [27]. The results of the study indicate that the combined intervention of a diet containing MCT and exercise has an additive effect on the reduction of body fat accumulation. Moreover, in recreational athletes, 2 weeks of ingesting food containing 6 g of MCTs per day suppressed increases in blood lactate concentration and the perception of exertion during moderate-intensity exercise. It also extends the duration of subsequent high-intensity exercise at levels higher than those achieved by ingestion of LCT-containing food [28].

The concept of a "structured lipid" implies modification of the fatty acids composition and/or their location in the glycerol backbone, and improvement of the physical and/or physiological properties of dietary lipids. Recently, structured medium-chain and long-chain triacylglycerols (MLCTs) containing MCFAs and long-chain fatty acids (LCFAs) in the same molecule have been developed by transesterification of MCTs with LCTs [29,30]. Feeding rats MLCT for 6 weeks reduced their body fat accumulation and increased their postprandial hepatic β-oxidation of fatty acids compared with LCT feeding [31,32]. Shinohara et al. reported that MLCT feeding suppressed lipogenesis (such as fatty acid synthase activity) and enhanced lipolysis (such as carnitine palmitoyltransferase activity and mRNA expression, uncoupling protein mRNA expression, and glycerol kinase mRNA expression) in adipose tissue [33]. The authors suggest that the altered fatty acid metabolism in adipose tissue *per se* was also responsible for the lowered adiposity by dietary MLCT. In a human study, healthy subjects consumed 14 g of MLCT containing 1.7 g of MCFAs daily at breakfast (as test oil-containing bread) for 12 weeks, and significant decreases in body weight, amount of body fat, subcutaneous and visceral fat were noted in the MLCT group at 8 weeks compared with the LCT group [34]. Other studies have also shown that consumption of MLCTs (as liquid formula diet or cooking oil) reduces body fat mass [35–38], which may be due to higher postingestive total energy expenditure than LCT consumption [39,40]. Because MCTs have a low smoking point, easily foam during deep frying and are expensive, their general uses have been limited. On the other hand, MLCTs have a higher smoking temperature and are therefore better for cooking than a physical mixture of MCTs and LCTs. Thus, structural conversion of MCTs to MLCTs broadens their range of uses and may attract more attention to MCFAs/MCTs functions [29,30]. In addition, Nagata et al. evaluated the nutritional and metabolic features of the highly purified structured lipids with a specific *sn*-positional distribution of MCFAs (C8–LCFA–C8, LCFA–C8–LCFA, C10–LCFA–C1 and LCFA–C10–LCFA) compared with corn oil in rats [41]. The results indicated that the feeding of long-chain–medium-chain–long-chain (L–M–L) types of structured lipids could effectively improve serum and liver lipid profiles and that M–L–M types may be a preferable substrate for the pancreas and contribute to energy supply in rats. The authors also evaluated the physiological function of structured lipids containing MCFAs and n-3 PUFAs (EPA–C8–C8, C8–EPA–C8, DHA–C8–C8 and C8–DHA–C8) compared with soybean oil in rats [42]. In the study, serum lipid levels were lowered by structured lipids and perirenal adipose tissue weight was lowered by D–8–8 and 8–D–8 treatment compared with those of soybean oil group. The results of these studies suggest that fatty acid species and the differences in intramolecular distribution of fatty acids in dietary TG affect the nutritional behavior of dietary lipids.

St-Onge et al. prepared a functional oil (FctO) that contained MCTs, plant sterols and n-3 PUFA-rich flaxseed oil [43,44]. Twenty-four overweight but otherwise healthy men consumed diets that contained either FctO or olive oil for 4 weeks, and the results indicated that consumption of FctO improves plasma lipid profiles, including reduced low-density-lipoprotein (LDL) cholesterol and increased peak LDL particle size [43]. The authors also reported that consumption of FctO for 27 days substantially lowered plasma total cholesterol and LDL cholesterol, but did not affect circulating triglyceride or HDL cholesterol in healthy, overweight women [44].

With respect to safety, diets containing MCFAs appear to be safe and well-tolerated in short-term and long-term clinical studies [45–48]. We propose that a variety of MCFA/MCT-containing structured lipids or blended oils would be useful in reducing cardiovascular disease risk through the combination of their various beneficial actions. Furthermore, future studies evaluating the effects of combinations of MCTs and various food factors (such as L-carnitine, sesamin and soybean protein) would be of great interests.

3. Physiological effects of MCFAs on diabetes and hypertension

Antidiabetic properties of MCTs in animals and humans have been reported [49–53]. Takeuchi et al. demonstrated that rats fed a diet containing MCT had less body fat accumulation and better glucose tolerance than rats fed a diet containing LCT [49]. Wein et al. reported that dietary LCFA clearly impair insulin sensitivity and lipid metabolism, but MCFA seem to protect from lipotoxicity and subsequent insulin resistance without caloric restriction in rats fed high amounts of fat [50]. Additionally, Turner et al. demonstrated that MCFA reduce adiposity and preserve insulin action in muscle and adipose, despite inducing steatosis and insulin resistance in the livers of mice and rats fed a high-fat diet [51].

In a human study, non-insulin-dependent diabetes patients and non-diabetic subjects were examined in a 5-day cross-over design, in which the short-term metabolic effects of a 40% fat diet containing 77.5% of fat calories as MCT were compared with an isocaloric LCT-containing diet [52]. The results indicated that consumption of MCT increased insulin-mediated glucose metabolism, as measured by the euglycemic clamp technique, in both diabetic ($30 \pm 9\%$ increase in glucose infusion rate (GIR)) and non-diabetic subjects (Normal subjects, $17 \pm 6\%$ increase in GIR; hypertriglyceridemic subjects, $30 \pm 9\%$ increase in GIR) compared with the LCT diet. Recently, Han et al. reported that the consumption of MCT at 18 g/day as part of daily food intake for 90 days resulted in reduced body weight, waist circumference and a homeostasis model assessment of insulin resistance in moderately overweight, subjects with type 2 diabetes [53]. Moreover, Page et al. reported that MCT ingestion improves cognition without affecting adrenergic or symptomatic responses to hypoglycemia in subjects with type 1 diabetes (intensively treated with insulin, $n = 11$) [54]. Although these studies suggest that MCTs offer the therapeutic advantage of preserving insulin sensitivity and/or brain function both in patients with type 1 or type 2 diabetes, very old data should be reassessed in a large-scale long-term clinical study.

Interestingly, Takeuchi et al. demonstrated that rats fed an MCT-containing diet had higher levels of adiponectin in their serum and adipose tissue compared with rats fed the LCT-containing diet [49]. Recent advances in molecular and cellular biology have shown that adipose tissue stores excess energy in the form of fat and plays an important role in regulating lipid and glucose homeostasis by secreting physiologically active substances called adipocytokines [55]. Adiponectin is one of the most abundant adipose-specific secretory proteins in rodents and humans [56,57]. The expression of adiponectin is reduced in obesity and blood levels are negatively correlated with abdominal fat accumulation [58–61]. Subjects with hypoadiponectinemia, caused by gene mutation of adiponectin, exhibit dyslipidemia and impaired glucose tolerance [62,63]. Adiponectin-null mice showed delayed clearance of non-esterified fatty acids in their plasma and severe diet-induced insulin resistance [64]. Several reports have indicated that adiponectin can lead to enhanced insulin action in vitro and in vivo by activating insulin-receptor substrate 1-associated phosphatidylinositol-3-kinase, AMP-activated protein kinase and peroxisome proliferator-activated receptor (PPAR)-alpha in liver and muscle [56,64–66], which strongly suggests that adiponectin has a protective role against insulin resistance. Takeuchi et al. also indicated that the antidiabetic effect of MCT with increased levels of plasma and adipocyte adiponectin was due to the enhanced expression of adiponectin mRNA in perirenal adipose tissue [49]. The authors showed that expression of transcriptional factors PPAR-gamma and retinoid X receptor (RXR) mRNA was increased simultaneously in adipose tissue, and they speculated that an increased amount of PPAR-gamma/RXR heterodimer enhanced the promoter activity of adiponectin in adipocytes. The function of MCTs as a dietary adiponectin inducer (dietary insulin sensitizer) will be of great interest in future studies.

MCFA/MCT administration does not seem to affect blood pressure [45,67,68]. Administration of MCFAs/MCTs, however, improved cardiac dysfunction, hypertrophy, and an impaired capacity to withstand an acute adrenergic stress despite persistent hypertension in spontaneously hypertensive rats [67–69]. These reports suggest the potential clinical benefits of MCFA/MCT therapy for the management of patients with cardiac diseases [70].

4. Concluding remarks

This review has explored the physiological functions and molecular actions of MCFAs/MCTs in the development of metabolic syndrome. Experimental studies demonstrate that dietary MCFAs/MCTs suppress fat deposition through enhanced thermogenesis and fat oxidation in animal and human subjects. Additionally, several reports suggest that MCFAs/MCTs offer the therapeutic advantage of preserving insulin sensitivity in animal models and patients with type 2 diabetes. The ability of MCFAs/MCTs to regulate the production of adipocytokines (e.g., adiponectin) will be of great interest in future studies.

Although further evaluations will be required to reach a consensus regarding the health benefits of MCFAs/MCTs on obesity and metabolic disorders because beneficial properties have not been apparent in some clinical trials [71], the therapeutic potential of MCFAs/MCTs against metabolic syndrome is still promising.

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