Preventive effects of medium-chain triglycerides supplementation on the oxidative capacity in skeletal muscle under cachectic condition

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ABSTRACT

Cachexia is a multifactorial condition characterized by muscle mass loss and induces metabolic dysfunction of the skeletal muscles. The preventive effects of medium-chain triglycerides (MCT) supplementation on the oxidative capacity in skeletal muscle under cachectic condition were investigated in the present study. ICR mice were randomly divided into four groups; control, lipopolysaccharide (LPS), LPS plus long-chain triglycerides (LCT) and LPS plus MCT supplementation. LCT and MCT oil were administered to the LPS + LCT and LPS + MCT groups orally (5.0 g/kg body weight/day) by a catheter for one week. Cachexia was induced in the LPS, LPS + LCT, and LPS + MCT groups via LPS injection (7.5 mg/kg body weight, i.p.) after the supplementation. LPS induced a reduction of ketone bodies concentration in blood plasma. LPS also induced a decrease in succinate dehydrogenase activity and PGC-1α expression level in tibialis anterior muscles. Meanwhile, MCT supplementation suppressed a decrease in ketone bodies concentration and succinate dehydrogenase activity. In addition, MCT supplementation increased the level of citrate synthase activity in the muscles. These results suggested the preventive effect of MCT supplementation on oxidative capacity in skeletal muscle and the involvements of ketone bodies regulation under cachectic condition.

INTRODUCTION

Cachexia is defined as a complex metabolic syndrome associated with underlying illness such as sepsis and cancer (Evans et al. 2008) and is associated with decreased oxidative capacity (Tappy and Chioléro 2007) and adenosine triphosphate synthesis rate in skeletal muscle (Brealey et al. 2002). Mitochondrial oxidative phosphorylation capacity depends on the mitochondrial enzyme activity and mitochondrial biogenesis in skeletal muscle (Short et al. 2003; White and Schenk 2012). Mitochondrial enzyme activity in the TCA cycle is highly associated with muscle performance (Holloszy 1967). Lipopolysaccharide (LPS) stimulation reduces mitochondrial enzyme activity (Tanaka et al. 2016), especially by inhibition of succinate dehydrogenase (SDH), one of the enzymes in the TCA cycle (Cordes et al. 2016).

Systemic endurance training (Holloszy 1967) and local muscle training (Kitaoka et al. 2016) are well
known as a countermeasure for improving the oxidative capacity of skeletal muscle. Local muscle training prevents decrement in muscle oxidative metabolism induced by LPS stimulation (Tanaka et al. 2016). However, it is difficult to do adequate training for cachectic patients due to the decrease in exercise capacity strictly.

Lipid supplementation is effective for enhancing mitochondrial oxidative phosphorylation capacity (Miller et al. 1984; Hancock et al. 2008; Schönfeld and Wojtczak 2016). Most lipids ingested as foods are triglycerides in which glycerol and three fatty acids are bound. Long-chain triglycerides (LCT), composed of 12 or more carbon atoms, and medium-chain triglycerides (MCT), composed of 8 to 10 carbon atoms, have different metabolic effects depending on the number of carbon atoms (Leyton et al. 1987). Long-term supplementation of LCT leads to the accumulation of body fat and induces side effects as insulin resistance (Han et al. 1997; Oakes et al. 1997; Buettner et al. 2006). In addition, LCT requires specific mitochondrial outer membrane enzymes to cross the mitochondrial membrane (Bach et al. 1996). It has been shown that LCT is hard to cross the mitochondrial membrane due to decreased mitochondrial outer membrane enzyme activities under cachectic condition (Eaton et al. 2003). Meanwhile, MCT has no side effects like LCT supplementation (Noguchi et al. 2002; St-Onge et al. 2003). MCT is rapidly metabolized in mitochondria compared with LCT because it is independent of mitochondrial outer membrane enzymes (Bach et al. 1996). In addition, dietary MCT increases ketone bodies production in the liver (Shinohara et al. 2005; Kojima and Kasai 2008, Nishimura et al. 2017). The previous study showed that ketone bodies supplementation facilitated the oxidative capacity in skeletal muscle under normal condition (Evans et al. 2017). Therefore, dietary MCT might prevent the decreased oxidative capacity in skeletal muscles under cachectic condition.

The purpose of the present study was to investigate the preventive effects of dietary MCT supplementation on the decreased oxidative capacity in skeletal muscle under LPS-induced cachectic condition. To understand the role of cachexia-induced oxidative capacity dysfunction and the preventive effects with LCT or MCT supplementation, we analyzed the mitochondrial oxidative enzyme activity, the PPAR-γ co-activator-1 α (PGC1-α) expression, and ketogenesis.

MATERIALS AND METHODS

Experimental animals. Twenty-seven adult male ICR mice (7 weeks old) weighing 32–34 g (Japan SLC, Hamamatsu, Japan) were used in this study. The mice were housed in a temperature-controlled room at 22 ± 2°C with a light-dark cycle of 12 h, and feed and water were given freely. The mice were randomly divided into four groups: control (CON, n = 6), LPS-induced cachexia (LPS, n = 7), LCT administered before LPS-induced cachexia (LPS + LCT, n = 7), and MCT administered before LPS-induced cachexia (LPS + MCT, n = 7) groups, after a week familiarization period. LCT and MCT oil were administered daily to the animals in the LPS + LCT and LPS + MCT groups orally by a catheter for a week (5.0 g/kg body weight/day). The animals in the CON and LPS groups were given the same volume of saline. After a week, the animals in the LPS, LPS + LCT, and LPS + MCT groups were injected LPS (7.5 mg/kg body weight, i.p.). The animals in the CON group were injected with the same volume of PBS.

This study was approved by the Institutional Animal Care and Use Committee and was performed according to the Kobe University Animal Experimentation Regulations. All experimental procedures and animal care were performed in accordance with the National Institutes of Health (NIH) Guidelines for Care and Use of Laboratory Animals (National Research Council, 1996).

Sample preparation. After 24 h from LPS injection, all animals were deeply anesthetized by injection of pentobarbital sodium (50 mg/kg, i.p.). After these injections, the tibialis anterior muscle and epididymal adipose tissue were removed and weighed. Blood was sampled from the inferior vena cava and centrifuged at 3,000 × g for 10 min at 4°C. The plasma samples were then collected. The tibialis anterior muscle was immediately frozen in an isopentane with dry ice. The plasma and muscle samples were stored at −80°C until histological and biochemical analyses. The tibialis anterior muscle, fat muscle fibers, has reported to cause mitochondrial dysfunction by LPS injection (Tanaka et al. 2016).

Total ketone bodies concentration. Total ketone bodies concentration in plasma was measured using the total ketone bodies assay kit (Wako, Tokyo, Japan). Briefly, it was determined by measuring the rate of formation of β-nicotinamide adenine dinucleotide, reduced form, produced from 3-hydroxybutyric acid.
and acetoacetic acid. Absorbance at 405 nm was measured with a spectrophotometer.

**Histological analysis.** Tibialis anterior muscles were cut into 10-μm sections from the middle region of the muscle belly using a cryostat (CM-1510S; Leica Microsystems, Mannheim, Germany) at −25°C and then mounted on glass slides. The sections were stained for hematoxylin-eosin (HE) and succinate dehydrogenase (SDH).

HE stain was used to determine muscle fiber cross-sectional area (CSA). A total of 1,200 fibers per each group (200 fibers per muscle sample) were analyzed from each sample. The sections were measured using the Image J software program (NIH, Bethesda, MD, USA).

SDH stain was used to determine the SDH activity, as previously described (Nagatomo et al. 2012). The SDH activity was also analyzed using the Image J software program (NIH). The SDH images were digitized as gray-scale images. The gray-scale was quantified as one of 256 gray levels in each pixel; gray level 0 was equivalent to 100% light transmission, and gray level 255 was equivalent to 0% light transmission. The mean optical density (OD) of all pixels, which indicate the SDH activity level, was determined using a calibration graphic tablet containing 21 gradient-density range steps and corresponding to diffused density values.

**Protein expression measurements.** Portions (~20 mg) of each tibialis anterior muscles were homogenized in the buffer, containing 20 mM Tris-HCl (pH 7.5), 1% NP-40, 1% sodium deoxycholate, 1 mM EDTA, 1 mM EGTA, 150 mM NaCl, and 1% (v/v) protease for mammalian tissue (Sigma-Aldrich, Saint Louis, MO, USA) and 1% (v/v) phosphatase inhibitor cocktail for mammalian tissue (Sigma-Aldrich). The homogenates were centrifuged at 15,000 ×g for 15 min at 4°C. Total protein concentration was determined with a protein determination kit (Bio-Rad, Hercules, CA, USA). The homogenates were solubilized in sample loading buffer (50 mM Tris-HCl pH 6.8, 2% sodium dodecyl sulfate, 10% glycerol, 5% β-mercaptoethanol, and 0.005% bromophenol blue) and boiled for 10 min at 80°C.

The protein samples (30 μg/lane) were separated by SDS polyacrylamide gel electrophoresis and then transferred to polyvinylidene fluoride membranes. The membranes were blocked for 1 h with Tris-buffered saline with Tween 20 containing 5% skimmed milk at room temperature. After blocking, the membranes were incubated with primary antibody against peroxisome proliferator-activated receptor γ coactivator 1-alpha (PGC-1α) (1 : 200 in TBST, sc-13067; Santa Cruz Biotechnology, TX, USA) overnight at 4°C. The membranes were then incubated for 1 h at room temperature with anti-rabbit IgG conjugated to horseradish peroxidase (GE Healthcare, Waukesha, WI, USA). The membranes were developed using a chemiluminescent reagent (ECL; GE Healthcare) and analyzed with an image reader (LAS-1000; Fujifilm, Tokyo, Japan). GAPDH was used as an internal control.

**Citrate synthase activity.** Citrate synthase activity was measured as previously described (Srere 1963). Briefly, supernatants were solubilized in reaction buffer containing 0.1 mM DTNB and 0.3 mM acetyl-CoA. The reaction was initiated by oxaloacetic acid (0.5 mM final concentration). Absorbance at 412 nm was measured with a spectrophotometer for 5 min.

**Statistical analysis.** The data are expressed as mean ± SEM. The statistical differences between the four groups in the other results were analyzed using a one-way analysis of variance (ANOVA) followed by Tukey-Kramer post hoc test. The statistical significance was set at \( P < 0.05 \).

**RESULTS**

**Food intake, body weight, epididymal adipose weight, muscle wet weight, and fiber CSAs**

Food intake after LPS injection was significantly lower in the LPS injected (LPS, LPS + LCT, and LPS + MCT) groups than in the CON group. The body weight in LPS, LPS + LCT, LPS + MCT groups was significantly lower than that in the CON group. In the epididymal adipose, muscle wet weight and the ratio of muscle wet weight to body weight, there were no significant differences among all groups. There were also no significant differences among groups for the CSAs of the tibialis anterior muscle (Table 1).

**Total ketone bodies concentration in plasma**

The level of total ketone bodies concentration in plasma was analyzed as indicators of ketogenesis in the liver. The ketone bodies concentration in the LPS and LPS + LCT groups was significantly lower than that in the CON group, whereas that in the LPS + MCT group was higher than that in the LPS and LPS + LCT groups (Fig. 1). These results suggest that LPS-induced cachexia induced a decrease
Protein expression levels of PGC-1α in skeletal muscle

Figure 3 shows the expression level of PGC-1α protein as a regulator of mitochondrial biogenesis in the tibialis anterior muscle. The expression levels of PGC-1α in the LPS, LPS + LCT, and LPS + MCT groups were significantly lower than that in the CON group. However, there were no significant differences among LPS injected groups. These results suggest that LPS resulted in a decrease in the expression level of PGC-1α protein, and MCT supplementation could not prevent the level of that under cachectic condition.

Citrate synthase activity in skeletal muscle

The citrate synthase activity in the LPS and LPS + LCT groups was no significantly different compared with that in the CON group, whereas that in the LPS + MCT group was higher than that in the CON, LPS and LPS + LCT groups (Fig. 4), suggesting that MCT supplementation promotes the citrate synthase activity even under cachectic condition.

DISCUSSION

The main findings in the present study are as follows: 1) dietary MCT supplementation prevented LPS-induced decreases in total ketone bodies concentration and SDH activity, and 2) increased citrate synthase activity in tibialis anterior muscle. These findings suggest that dietary MCT supplementation prevents a decrease in the oxidative capacity of skeletal muscle under cachectic condition.

In the present study, the levels of total ketone bodies concentration in plasma decreased under the LPS-induced cachetic condition. Most ketone bodies are synthesized by the mitochondria in the liver.

Table 1 Food intake, body weight, adipose weight, muscle weight, and fiber CSA

|                | CON     | LPS     | LPS + LCT | LPS + MCT |
|----------------|---------|---------|-----------|-----------|
| Food intake    |         |         |           |           |
| Before LPS (g/day) | 5.2 ± 0.2 | 5.4 ± 0.3 | 4.8 ± 0.3  | 4.5 ± 0.2 |
| After LPS (g/day)  | 5.3 ± 0.3 | 0.4 ± 0.1*| 0.4 ± 0.1* | 0.4 ± 0.1*|
| Body weight     | 39.2 ± 0.9| 36.0 ± 0.5*| 34.0 ± 1.0*| 36.0 ± 0.6*|
| Epididymal adipose weight (mg) | 735 ± 106 | 721 ± 53  | 678 ± 99  | 619 ± 100 |
| Tibial anterior muscle |        |         |           |           |
| Muscle wet weight (mg) | 58.4 ± 1.5 | 57.1 ± 1.5 | 58.0 ± 1.8 | 59.3 ± 1.0 |
| Muscle to body weight ratio (mg/g) | 1.50 ± 0.06 | 1.59 ± 0.05 | 1.72 ± 0.08 | 1.65 ± 0.04 |
| Fiber CSA (µm²) | 2210 ± 110| 1899 ± 77 | 2178 ± 52 | 2221 ± 125 |

Values indicate means ± SEM. CON: control group (n = 6), LPS: cachexia induced by lipopolysaccharide group (n = 7), LPS + LCT: lipopolysaccharide plus long-chain triglycerides (n = 7), LPS + MCT: lipopolysaccharide plus medium-chain triglycerides (n = 7). The symbol * indicates a significant difference compared with the CON group at P < 0.05.

in total ketone bodies in plasma, and MCT supplementation prevented the level of total ketone bodies under cachectic condition.

SDH activity in skeletal muscle

The SDH activity in the LPS and LPS + LCT groups was significantly lower than that in the CON group, whereas that in the LPS + MCT group was higher than that in the LPS and LPS + LCT groups (Fig. 2). Thus, the level of SDH activity in LPS-induced skeletal muscle decreased, and MCT supplementation inhibited the level of that in cachectic muscle.

Fig. 1 Total ketone bodies concentration in plasma. CON: control group (n = 6), LPS: cachexia induced by lipopolysaccharide group (n = 7), LPS + LCT: lipopolysaccharide plus long-chain triglycerides (n = 7), LPS + MCT: lipopolysaccharide plus medium-chain triglycerides (n = 7). Values indicate means ± SEM. The symbol *, †, and ‡ indicate significant difference compared with the CON, LPS, and LPS + LCT groups at P < 0.05, respectively.
Therefore, it is suggested that the decrease in total ketone bodies is due to the suppression of ketogenesis in the liver by LPS in the present study. Meanwhile, MCT supplementation inhibited the LPS-induced decrease in total ketone bodies concentration in plasma, while LCT failed to inhibit that in the present study. LCT is absorbed from the small intestine, incorporated into chylomicron and reaches the systemic circulation via the lymph system. MCT (Laffel 1999, Newman and Verdin 2014), and LPS stimulation inhibits the ketogenesis (Takeyama et al. 1989, 1990). LPS stimulation causes liver injury by inflammatory cytokines (Su 2002), and also reduces mitochondrial function in the liver (Kono et al. 2003). Therefore, it is suggested that the decrease in total ketone bodies is due to the suppression of ketogenesis in the liver by LPS in the present study.
is absorbed from the small intestine, not incorporated into chylomicron because of a water-soluble and smaller molecule size and reaches the liver via the portal vein (Bach et al. 1996). MCT is metabolized in the liver and increases the level of total ketone bodies in plasma (Shinohara et al. 2005; Kojima and Kasai 2008; Nishimura et al. 2017). Kojima and Kasai (2008) have reported that ketone bodies concentration in plasma was increased by ingesting MCT under malnourished condition for two weeks in rats, which is similar to the results of the present study. Thus, MCT would maintain the ketogenesis in the liver by efficiently supplying the source of the ketone bodies to the liver.

MCT supplementation maintained the level of SDH activity in the tibialis anterior muscle under the LPS-induced cachectic condition in the present study. Cordes et al. (2016) have reported that LPS stimulation increases succinate levels by inhibition of SDH. Thus, it has been known that LPS stimulation increases itaconate and inhibits SDH in the mitochondrial TCA cycle (Cordes et al. 2016; Langston et al. 2017). Meanwhile, MCT supplementation attenuated the LPS-induced decrease in SDH activity in skeletal muscle although LCT failed to attenuate that in the present study. Montgomery et al. (2013) have reported that medium-chain fatty acids treatment increases the SDH activity in C2C12 myotubes, which is consistent with the results of the present study. Ketone bodies are synthesized in the liver and efficiently transported to skeletal muscle, become an energy source of the TCA cycle by being converted into acetyl-CoA in the transported tissue (Laffel 1999; Newman and Verdin 2014). Cox et al. (2016) have reported that the ingestion of ketone ester-based drinks increases ketone bodies in the blood and skeletal muscle. This study has shown that the increase in ketone bodies decreased glycolysis and increased endurance performance with increased oxidative capacity in skeletal muscle. Therefore, it is suggested that MCT supplementation increases SDH activity in the TCA cycle by increasing the energy source by utilizing ketone bodies in skeletal muscle.

PGC-1α is one of the regulators of mitochondrial biogenesis (Ventura-Clapier et al. 2008). Several studies have shown that the mitochondrial biogenesis was decreased in skeletal muscle under cachectic condition (Menconi et al. 2010; White et al. 2011; Tanaka et al. 2016). In the present study, the expression level of PGC-1α protein in the tibialis anterior muscle was decreased under the LPS-induced cachectic condition, and LCT and MCT failed to inhibit a decrease in the expression level of PGC-1α protein. Hancock et al. (2008) have reported that high-fat diets increase PGC-1α protein expression level for 4 weeks, but not changes it for 1 or 2 weeks in mice. Thus, the expression level of PGC-1α protein might not change for 1 week supplementation. It would be necessary for a long-term supplementation to increase the expression level of PGC-1α by LCT or MCT supplementation.

In the mitochondrial enzyme activity, the citrate synthase activity in the LPS + MCT group was higher than that in the LPS group. Previous studies have reported that MCT supplementation increased the citrate synthase activity in mice or rats under normal condition (Turner et al. 2009; Ishizawa et al. 2015). In the present study, MCT supplementation was administered to the rats for 1 week before LPS injection. MCT supplementation might have increased the citrate synthase activity before LPS injection, and the activity maintained after LPS injection. Meanwhile, LPS did not decrease citrate synthase activity, unlike in SDH activity in the present study. Previous studies have reported that citrate synthase activity increased in early phases within 4 h of LPS injection (Fredriksson et al. 2009; Ozkok et al. 2014). Conversely, Tanaka et al. (2016) have reported that citrate synthase activity was decreased in severe sepsis model with repeated LPS injection for 4 days. Thus, the change of citrate synthase activity by LPS may be determined by the severity or elapsed-time after LPS injection. In addition, Cordes et al. (2016) have reported that LPS caused the succinate accumulation by inhibition of SDH but did not change citrate level, suggesting the no effect on citrate synthase activity by LPS. While this point could be a reason for the discrepancy about the reaction to LPS between citrate synthase and SDH activities, we need further experiments using ketogenesis inhibition with MCT treatments to know the detailed mechanism.

In conclusion, we demonstrated that dietary MCT supplementation could inhibit the LPS-induced metabolic aberration in ketone bodies and decreased oxidative capacity in skeletal muscle. These results suggested that dietary MCT supplementation might have the potential to become an effective therapeutic intervention for the prevention of oxidative capacity dysfunction in skeletal muscle under cachectic condition.

CONFLICT OF INTEREST
The authors have no conflict of interest to disclose.
Effects of MCT on cachectic muscle

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