Medium-Chain Triacylglycerol Suppresses the Decrease of Plasma Albumin Level through the Insulin-Akt-mTOR Pathway in the Livers of Malnourished Rats

Seiji SEKINE, Shin TERADA and Toshiaki AYAMA

Central Research Laboratory, The Nisshin OilliO Group, Ltd.,
1 Shinmei-cho, Yokosuka, Kanagawa 239–0832, Japan

(Received August 30, 2012)

Summary  Recent studies have shown that medium-chain triacylglycerol (MCT) improved serum albumin concentration in elderly people with protein-energy malnutrition (PEM) and in malnourished rats. However, the mechanism for this effect has not been clarified. Dietary MCT promotes insulin secretion from the pancreas, and insulin activates mammalian target of rapamycin (mTOR) complex 1 (mTORC1) via the activation of phosphoinositide 3-kinase (PI3K) and its downstream effector, Akt. mTORC1 promotes mRNA translation through S6K and 4E-BP1. Therefore, we hypothesized that dietary MCT elevates albumin synthesis through promotion of insulin-Akt-mTOR transduction in the liver. To test this hypothesis, we measured phosphorylated Akt, mTOR and albumin in the livers of malnourished rats. In the present study we examined rats fed low-protein diets containing either MCT or long-chain triacylglycerol (LCT) with energy restriction. The plasma and liver albumin levels were significantly higher in the MCT-fed group than in the LCT-fed group. In addition, plasma insulin concentration, liver phosphorylated Akt/Akt and phosphorylated mTOR/mTOR levels were significantly higher in the MCT-fed group than in the LCT-fed group. These results suggest that one of the mechanisms for the albumin improvement effect of dietary MCT is the promotion of albumin synthesis through the insulin-Akt-mTOR signaling pathway of the liver.

Key Words  protein-energy malnutrition, insulin, Akt, mTOR, albumin

Medium-chain triacylglycerol (MCT) has been utilized for improvements of nutritional and energy statuses in preterm infants (1) and in patients with a variety of malabsorptive disorders (2) since the 1960s, because MCT is rapidly digested and absorbed in the gastrointestinal tract. On the other hand, in elderly people, digestion and absorption are delayed by aging, and energy intake is decreased by decreased physical activity. Most elderly people, especially those residing in nursing homes and hospitals, tend to suffer from protein-energy malnutrition (PEM) (3).

PEM status is indicated by hypoalbuminemia. Albumin is synthesized in the liver, and serum albumin is a major component of serum protein, which sustains osmotic pressure and transports many kinds of substances or hormones to organs. Serum albumin has been the most common index of nutritional status. Its concentration in serum is influenced by many factors independent of nutritional factors, such as infections, trauma (by an increase in the transcapillary escape rate of albumin), hydration status (by haemodilution), liver function (by a decrease in synthesis) and kidney disease (by albumin losses).

In previous studies, dietary MCT improved serum albumin concentration in elderly people with PEM (4) and in malnourished rats (5, 6). Nitrogen balance was also improved by dietary MCT (5, 7). Kojima and Kasai hypothesized that improvement of protein balance with MCT intake occurred through suppression of gluconeogenesis, which mainly started from body protein degradation. However, gluconeogenic enzymes were not changed in malnourished rats fed MCT (6). Therefore, the mechanism for the albumin improvement effect of dietary MCT is not yet clear. The results of previous studies indicated that dietary MCT increases serum insulin concentration in the rats (6, 8, 9) and humans (7, 10). One of the main properties of MCT is its ketogenic character (8, 11, 12). Madison et al. reported that ketone bodies have a direct stimulatory effect on the pancreatic beta cells (13). Insulin and other growth factors activate mammalian target of rapamycin (mTOR) complex 1 (mTORC1) via the activation of phosphatidylinositol 3-kinase (PI3K) and its downstream effector, Akt (also called protein kinase B) (14, 15). Active mTOR enhances cell growth by promoting mRNA translation and increasing cell mass (16, 17). Ijichi et al. reported that branched-chain amino acids promote albumin synthesis in rat hepatocytes through the mTOR signal transduction system (18). Because mTOR might relate to albumin synthesis, we hypothesized that one of the mechanisms for the albumin improvement effect of dietary MCT is related to the insulin-Akt-mTOR signal transduction system. To clarify the albumin improvement mechanism of MCT, in the present study we evalu-
ated the effects of dietary MCT on the insulin-Akt-mTOR transduction system in malnourished rats.

**MATERIALS AND METHODS**

**Animals and diets.** All animals were treated in accordance with the guidelines for the care and use of laboratory animals (Notification of the Prime Minister’s Office in Japan). The experimental plan was approved by the Laboratory Animal Care Committee of the Research Laboratory, The Nisshin OilliO Group, Ltd.

Three-week-old male Wistar rats (Japan SLC, Inc., Shizuoka, Japan) weighing 40–50 g were individually housed in stainless steel wire cages and allowed free access to sterilized water. The temperature of the animal room was set at 23±1°C, with a humidity of 50±5% and illumination from 08:00 to 20:00 h. In the taming period, rats were allowed free access to an AIN-93G-based diet (19).

After taming for 3 d, the rats were randomized into two groups (n=10). The malnourished rats were fed modified AIN-93G diet (Table 1) in an amount that was 60% of the ad libitum intake. The modified AIN-93G diet contains 5% protein. The fatty acid composition of the test lipids is shown in Table 1. Rats in these groups were maintained for 15 d. On days 0 and 7, blood was drawn from the tail vain. At the end of the test period (day 15), the rats were killed by bleeding under anesthesia with diethyl ether. Rats were not deprived of food before sacrificing. Blood was collected, and livers were removed. Heparin sodium was used as an anticoagulant, and plasma was separated by centrifugation at 2,700 g for 15 min at 4°C. Livers were frozen using liquid nitrogen and stored at −80°C until analysis.

**Fatty acid composition of test lipids.** Test lipids were saponified in 0.5 mol/L sodium hydroxide in methanol for 7 min at 100°C to liberate free fatty acids and then cooled on ice. After saponification, 2 mL of 14% boron trifluoride in methanol was added to fatty acid sodium salts solution, and the mixture was methylated for 15 min at 100°C. Fatty acid methyl esters were extracted using n-hexane. Fatty acid derivatives were analyzed by gas-liquid chromatography using a GC-2014 (Shimadzu, Kyoto, Japan) equipped with a capillary column (OMEGAWAX™ 250, 30 m long, 0.25 mm internal diameter, 0.25 μm thickness; Supelco, Inc., Bellefonte, PA, USA).

**Measurement of plasma albumin and total protein concentrations.** Plasma albumin concentration was measured by the bromocresol green (BCG) method (A/G B-Test Wako; Wako Pure Chemical Industries, Ltd., Osaka, Japan). Total protein concentration was measured by the biuret test (A/G B-Test Wako; Wako Pure Chemical Industries).

**Analysis of plasma insulin concentration.** Plasma insulin concentration was analyzed with an enzyme immunoassay kit (Mercodia AB, Uppsala, Sweden).

**Western blot analysis.** For Western blotting of cytosolic proteins, frozen, powdered tissue was homogenized in 20 volumes of radioimmunoprecipitation assay (RIPA) buffer (Millipore, MA, USA) containing protease and phosphatase inhibitor cocktail (Thermo Scientific, IL, USA) with a Polytron homogenizer. The homogenate was centrifuged at 10,000 × g for 10 min at 4°C, and the pellet was discarded. The protein concentrations of supernatant were determined with a Protein Assay Rapid Kit (Wako Pure Chemical Industries). Ten micrograms of proteins were fractionated in a 7.5% polyacrylamide gel and transferred onto a polyvinylidene difluoride membrane (Immobilon P; Millipore) by electroblotting. After blocking for 1 h, the membrane was incubated overnight at 4°C with a primary antibody: anti-phosphorylated Akt Ser473 (Cell Signaling Technology, MA, USA); anti-Akt (Cell Signaling Technology); anti-phosphorylated mTORSer2448 (Abcam, Cambridge, UK); anti-mTOR (Cell Signaling Technology); or anti-albumin (Santa Cruz Biotechnology, CA, USA). These primary antibodies were diluted 1:4,000. We used immunoreaction enhancer solution (Can Get Signal; Toyobo, Osaka, Japan) for the detection of phosphorylated protein.

After washing with a Tris buffer saline-Tween 20 solution, each membrane was incubated for 1 h at room temperature with the corresponding horseradish peroxidase-conjugated secondary antibody (HRP-Goat Anti-Rabbit IgG (H+L); Invitrogen, CA, USA) at 1:20,000 dilution. Specific bands were detected using an enhanced chemiluminescence (ECL) Advance Western Blotting Detection Kit (GE Healthcare Japan, Tokyo, Japan) and a

---

**Table 1. Composition of the experimental diets (g/kg diet) and fatty acid composition (g/100 g fatty acids) of dietary lipids.**

|        | LCT                  | MCT                  |
|--------|----------------------|----------------------|
| Basic components1 | 900.0 | 900.0 |
| Test lipids2       | 70    | 70    |
| Soybean oil        | 70    | 10    |
| MCT                | —     | 60    |
| Fatty acids        |       |       |
| C8:0               | —     | 65    |
| C10:0              | —     | 19.1  |
| C14:0              | 0.1   | 0.1   |
| C16:0              | 11.2  | 2.8   |
| C18:0              | 3.3   | 0.6   |
| C18:1n-9           | 21.6  | 3.2   |
| C18:2n-6           | 56.6  | 8.3   |
| C18:3n-3           | 6     | 0.8   |
| C20:0              | 0.4   | 0.1   |
| C20:1n-9           | 0.3   | —     |
| C22:0              | 0.4   | 0.1   |
| C24:0              | 0.1   | —     |
| Total              | 100   | 100   |

1The basic components of the diet given to all groups were as follows (g/kg): cornstarch 547.486; casein 50; dextrinized cornstarch 132; cellulose powder 50; mineral mix (AIN-93G-MX) 35; vitamin mix (AIN-93-VX) 10; l-cystine 3; choline bitartrate 2.5; tert-butylhydroquinone (TBHQ) 0.014.
2Soybean oil and MCT were purchased commercially (The Nisshin OilliO Group, Tokyo, Japan).
Table 2. Body weight, body weight gain, food intake, energy intake, liver and right leg skeletal muscle weights in the malnourished rats fed LCT or MCT.

|                | LCT     | MCT     |
|----------------|---------|---------|
| Final body weight (g) | 53.98±0.72 | 53.4±0.46 |
| Body weight gain (g/d)  | 0.91±0.04  | 0.87±0.04 |
| Food intake (g/d)      | 6.22±0.07  | 6.21±0.06 |
| Energy intake (kcal/d) | 25.08±0.27 | 24.79±0.23 |
| Liver weight (g/100 g body weight) | 4.88±0.15 | 5.62±0.09*** |
| Skeletal muscle weight (g/100 g body weight) | 0.58±0.01 | 0.62±0.02 |

Values are the mean±SE, n=10.
Skeletal muscle weight of right leg is a sum of soleus, gastrocnemius and plantaris muscle.
***p<0.001 versus LCT-fed group (Student’s t-test).

Table 3. Plasma albumin, total protein and insulin concentrations in the malnourished rats fed LCT or MCT.

|                | LCT     | MCT     |
|----------------|---------|---------|
| Albumin (g/dL) |         |         |
| Day 0          | 3.58±0.03 | 3.57±0.04 |
| Day 7          | 2.88±0.06 | 3.11±0.06* |
| Day 15         | 2.56±0.05 | 2.89±0.04*** |
| Total protein (g/dL) |         |         |
| Day 0          | 5.13±0.12 | 5.15±0.11 |
| Day 7          | 4.49±0.1  | 4.59±0.04 |
| Day 15         | 3.83±0.21 | 4.43±0.18* |
| Insulin (pmol/L) |         |         |
| Day 15         | 203±37.8 | 382±50.1* |

Values are the mean±SE, n=10.
*p<0.05, ***p<0.001 versus LCT-fed group (Student’s t-test).

RESULTS

**Body weight, body weight gain, food intake, energy intake, liver and skeletal muscle weights**

Table 2 shows the body weight, body weight gain, food intake and energy intake in malnourished rats. Body weights increased slightly in response to both the long-chain triacylglycerol (LCT) and MCT diets, and no significant differences in the final body weight or body weight gain were observed between the two groups. Nor did food intake and energy intake differ significantly between the LCT-fed and the MCT-fed groups. Liver weight in the MCT-fed group was significantly higher than in the LCT-fed group. Skeletal muscle of the right leg tended to be higher in the MCT-fed group than in the LCT-fed group, but there was no significant difference (p=0.10).

**Plasma albumin, total protein and insulin concentrations**

Plasma albumin, total protein and insulin concentrations in the LCT-fed and MCT-fed rats were determined, and the results are shown in Table 3. Plasma albumin and total protein concentrations in the LCT-fed and MCT-fed groups were the same. On days 7 and 15, the plasma albumin concentration was significantly higher in the MCT-fed group than in the LCT-fed group. On day 7, plasma total protein concentration did not differ between the groups. On day 15, plasma total protein was higher in the MCT-fed group than in the LCT-fed group.

At the end of the experimental period (day 15), plasma insulin concentration was 88% higher in the MCT-fed group compared with the LCT-fed group. **Akt, mTOR and albumin in the liver**

As shown in Fig. 1, the phosphorylated Akt/Akt level was 29% higher in the MCT-fed group compared with the LCT-fed group (Fig. 1A). The phosphorylated mTOR/mTOR level was also 30% higher in the MCT-fed group.
compared with the LCT-fed group (Fig. 1B). The liver albumin level was 34% higher in the MCT-fed group compared with the LCT-fed group (Fig. 1C).

**Correlation of albumin synthesis factors**

As shown in Fig. 2, there was a significant positive correlation between plasma insulin concentration and liver phosphorylated Akt/Akt ($r=0.552$, $p<0.05$) (Fig. 2A), and phosphorylated Akt/Akt was positively correlated with liver phosphorylated mTOR/mTOR ($r=0.552$, $p<0.05$) (Fig. 2B). There was a significant positive correlation between phosphorylated mTOR/mTOR and liver albumin ($r=0.672$, $p<0.05$) (Fig. 2C), and liver albumin was positively correlated with plasma concentration ($r=0.478$, $p<0.05$) (Fig. 2D).

**DISCUSSION**

Previous studies showed that dietary MCT improved serum albumin concentration in malnourished rats (5, 6) and in elderly people with PEM status (4). However, the mechanism for this effect of dietary MCT was not clarified. In the present study we attempted to clarify the albumin improvement mechanism by dietary MCT in rats fed a low-protein diet with restricted energy intake.

Albumin is synthesized in the liver as preproalbumin, which has an N-terminal peptide that is removed before the nascent protein is released from the rough endoplasmic reticulum. The product, prealbumin, is in turn cleaved in the Golgi vesicles to produce the secreted form of albumin. It is known that fasting or feeding a low-protein diet rapidly induces a sharp decrease in albumin production in both humans (20, 21) and rats (22). The present study also showed that plasma albumin concentration was decreased in the malnourished rats fed a low-protein diet (Table 3). Kirsch et al. reported that there was an immediate decrease in the rate of albumin synthesis when the dietary protein intakes of malnourished and recovered patients were decreased (23). Therefore, the plasma albumin concentration of malnourished rats might be reduced by the decrease in albumin synthesis in this study. However, dietary MCT in the malnourished rats did not recover to the normal albumin level because the albumin concentration of normal rats is $3.59\pm0.04$ mg/dL.

The malnourished state has long been recognized as a potential precipitating factor in the development of hypoalbuminemia (24). When serum albumin decreased by 1 g/L, the odds of being classified as malnourished increased 1.1-fold (25); thus, serum albumin is a marker of nutrition status (26). The present study showed that dietary MCT improved plasma albumin concentration compared with LCT (Table 3), similar to the results of a previous study (5, 6). In addition, the liver albumin level was higher in the MCT-fed group than in the LCT-fed group (Fig. 1C). Because liver albumin positively correlated with plasma concentration (Fig. 2D), increased liver albumin might relate to improvement of plasma albumin by dietary MCT. The correlation coefficient between plasma and liver albumin was lower than for other combinations. Individual differences in albumin consumption may be large because albumin in the blood is consumed in various tissues. Therefore, the correlation coefficient between plasma and liver albumin levels may be low. In this study, liver weight in the MCT-fed group was higher than in the LCT-fed group. Skeletal muscle in the MCT-fed group was also higher than in the LCT-fed group. These phenomena suggest that the nutrition status of malnourished rats might be improved by dietary MCT.

Nosaka et al. showed that serum cholesterol concentration is also increased by dietary MCT (4) in elderly people with PEM. Like albumin, cholesterol is synthesized mainly in the liver, and both albumin and cholesterol reflect the liver synthesis function (27). Because the liver synthesis function might be promoted by dietary MCT, we focused on the activation of protein synthesis in the livers of rats fed MCT.

It has been shown that mTOR promotes protein synthesis through the promotion of mRNA translation by S6K and 4E-BP1 (28). A previous study indicated that albumin synthesis was promoted through the mTOR signal pathway by branched-chain amino acids (18). In this study, phosphorylated mTOR/mTOR positively correlated with liver albumin (Fig. 2C), and phosphorylated mTOR/mTOR was elevated in the MCT-fed group (Fig. 1B). These results indicated that activation of mTOR might be related to the increase in albumin by dietary MCT. Moreover, dietary amino acids might be efficiently utilized by the activation of mTOR, because dietary MCT improved the nitrogen balance in rats (5) and humans (7).

Insulin and IGF1 activate their cognate receptors, which in turn activate PI3K through the IRS proteins. PI3K phosphorylates PIP2 to PIP3. Akt is activated by binding to PIP3 and subsequent translocation to plasma...
Effect of Dietary MCT on Protein Metabolism

Membrane. Active Akt inhibits TSC1/2 and activates mTORC1 (15, 16, 29). In the current study, there was positive correlation between insulin and phosphorylated Akt/Akt (Fig. 2A), and between phosphorylated Akt/Akt and phosphorylated mTOR/mTOR (Fig. 2B). Moreover, insulin (Table 3) and phosphorylated Akt/Akt (Fig. 1A) were increased by dietary MCT. Therefore, increases in insulin and Akt activation by dietary MCT might be closely related to mTOR activation.

Medium-chain fatty acids, generated by MCT hydrolysis, are metabolized rapidly in mitochondria and yield a large amount of acyl-CoA, which is converted to ketone bodies and released to the blood (30). MacDonald et al. reported that β-hydroxybutyrate potentiated glucose-induced insulin release in fresh rat pancreatic islets (31). In the present study, the plasma glucose level might be higher than for fasting rats because the rats were killed without food deprivation. Kojima and Kasai (6) reported that dietary MCT increases serum ketone bodies which are acetoacetate and β-hydroxybutyrate in the malnourished rats. In our study, because both β-hydroxybutyrate and glucose concentration might be elevated in the MCT-fed group, the plasma insulin concentration was higher in the MCT-fed group than in the LCT-fed group. Insulin secretion is known to be regulated by glucose-dependent insulinotropic polypeptide (GIP), one of gut-derived insulinotropic agents (32). In this context, MCT has not been found effective in stimulating GIP release (33). It is known that serum free fatty acid (FFA) and glycerol are both useful indicators of lipolytic activity. Serum FFA concentration might rise in the MCT-fed group because FFA was higher in the MCT-fed group than in the LCT-fed group in the previous study (6). GPR40 is highly expressed in pancreatic β-cells, and GPR40 agonists augment insulin secretion. MCFAs are also GPR40 agonists. Therefore, FFA of MCFAs may promote insulin secretion through GPR40 of the pancreas. Therefore, the increase in plasma insulin concentration by dietary MCT might be attributed to direct stimulatory effects of medium-chain fatty acids (34) and/or of ketone bodies on β-cell islets (11).

Accordingly, the mechanism for the albumin improve-

ment effect of dietary MCT might be the promotion of albumin synthesis through the insulin-Akt-mTOR signaling pathway (Fig. 3). On the other hand, previous studies showed that albumin mRNA concentration and albumin synthesis are increased by insulin (35–38). Therefore, the albumin improvement effect by dietary MCT may also be attributable to direct albumin mRNA expression through increased plasma insulin concentration.

Our previous study suggested that dietary MCT might increase insulin stimulation by increasing the plasma adiponectin concentration (39). An increase in insulin stimulation by dietary MCT might improve plasma albumin concentration through activation of the insulin-Akt-mTOR signaling pathway.

In summary, the current study showed increasing insulin, phosphorylated Akt/Akt, phosphorylated mTOR/mTOR, liver albumin level and plasma albumin concentration in the malnourished rats fed MCT. These results suggest that one of the mechanisms for the albumin improvement effect of dietary MCT is the promotion of albumin synthesis through the insulin-Akt-mTOR transduction system in the liver.

Acknowledgments

We would like to thank Mrs. Yumiko Ishikawa for her conscientious assistance with animal care.

REFERENCES

1) Yamashita F, Shibuya S, Funatsu I, Kuno T, Ide H. 1969. Absorption of medium chain triglyceride in the low-birth-weight infant and nutritional evaluation of MCT milk formula for low-birth-weight infants using the Latin square technique. Kurume Med J 16: 191–201.
2) Scheig R. 1968. Absorption of dietary fat: use of medium-chain triglycerides in malabsorption. Am J Clin Nutr 21: 300–304.
3) Nakamura H, Fukushima H, Miwa Y, Shiraki M, Gomi I, Saito M, Mawatari K, Kobayashi H. 2006. A longitudinal study on the nutritional state of elderly women at a nursing home in Japan. Intern Med 45: 1113–1120.
4) Nosaka N, Adachi K, Kawashima Y, Suzuki H, Hayashi S, Aoyama T, Nakamura T. 2010. Effect of ingestion
of medium-chain fatty acids on serum albumin in the elderly with protein-energy malnutrition (PEM). J Jpn Soc Clin Nutr 32: 52–61.

5) Kojima K, Ogawa A, Nakamura R, Kasai M. 2008. Effect of dietary medium-chain triacylglycerol on serum albumin and nitrogen balance in malnourished rats. J Clin Biochem Nutr 42: 45–49.

6) Kojima K, Kasai M. 2008. Effects of dietary medium-chain triacylglycerol on mRNA level of gluconeogenic enzymes in malnourished rats. J Nutr Sci Vitaminol 54: 507–510.

7) Jiang ZM, Zhang SY, Wang XR, Yang NF, Zhu Y, Wilmore D. 1993. A comparison of medium-chain and long-chain triglycerides in surgical patients. Ann Surg 217: 175–184.

8) Yeh YY, Zee P. 1976. Relation of ketosis to metabolic changes induced by acute medium-chain triglyceride feeding in rats. J Nutr 106: 58–67.

9) Ooyama K, Kojima K, Aoyama T, Takeuchi H. 2009. Decrease of food intake in rats after ingestion of medium-chain triglyceride. J Nutr Sci Vitaminol 55: 423–427.

10) Chen FM, Wang JY, Sun LC, Juang RF, Huang TJ, Hsieh JS. 2005. Efficacy of medium-chain triglycerides compared with long-chain triglycerides in total parenteral nutrition in patients with digestive tract cancer undergoing surgery. Kaohsiung J Med Sci 21: 487–494.

11) Wiley JH, Leveille GA. 1973. Metabolic consequences of dietary medium-chain triglycerides in the rat. J Nutr 103: 829–835.

12) Guy DG, Tuley RJ. 1981. Effect of diets high carbohydrate, soy oil, medium-chain triglycerides or triglycerin on blood and liver lipid and glucose intermediates in meal-eating rats. J Nutr 111: 1437–1445.

13) Madison LL, Mebane D, Unger RH, Lochner A. 1964. The hypoglycemic action of ketones. II. Evidence for a stimulatory feedback of ketones on the pancreatic beta cells. J Clin Invest 43: 408–415.

14) Gingras AC, Kennedy SG, O’Leary MA, Sonenberg N, Madison LL, Mebane D, Unger RH, Lochner A. 1964. The hypoglycemic action of ketones. II. Evidence for a stimulatory feedback of ketones on the pancreatic beta cells. J Clin Invest 43: 408–415.

15) Blaskar PT, Hay N. 2007. The two TORCs and Akt. Dev Cell 12: 487–513.

16) Yang Q, Guan KL. 2007. Expanding mTOR signaling pathway. Genes Dev 12: 502–513.

17) Bhaskar PT, Hay N. 2007. The two TORCs and Akt. Dev Cell 12: 487–512.

18) Yeh YY, Zee P. 1976. Relation of ketosis to metabolic changes induced by acute medium-chain triglyceride feeding in rats. J Nutr 106: 58–67.

19) Martins LD, Leveille GA. 1973. Metabolic consequences of dietary medium-chain triglycerides in the rat. J Nutr 103: 829–835.

20) Guy DG, Tuley RJ. 1981. Effect of diets high carbohydrate, soy oil, medium-chain triglycerides or triglycerin on blood and liver lipid and glucose intermediates in meal-eating rats. J Nutr 111: 1437–1445.

21) Madison LL, Mebane D, Unger RH, Lochner A. 1964. The hypoglycemic action of ketones. II. Evidence for a stimulatory feedback of ketones on the pancreatic beta cells. J Clin Invest 43: 408–415.