

Review

Diacylglycerol oil for the metabolic syndrome

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Abstract

Excess adiposity has been shown to play a crucial role in the development of the metabolic syndrome. The elevated fasting and postprandial triglyceride-rich lipoprotein levels is the central lipoprotein abnormality observed in the metabolic syndrome. Recent studies have indicated that diacylglycerol, a natural edible oil, is effective for fasting and postprandial hyperlipidemia and for obesity prevention. Therefore, we will here discuss the mechanisms of diacylglycerol-mediated improvements in hyperlipidemia and diacylglycerol-mediated obesity prevention, and effects of diacylglycerol oil on lipid/glucose metabolism and on body fat. Further, the therapeutic application for the metabolic syndrome will be considered.

Introduction

Visceral fat accumulation has been shown to play a crucial role in the development of the metabolic syndrome, which is highly atherogenic. Dyslipidemia associated with the metabolic syndrome are elevated fasting and postprandial triglyceride (TG)-rich lipoproteins, decreased high-density lipoprotein (HDL), and increased small dense low-density lipoprotein (LDL) [1]. Insulin resistance resulting from obesity, increases very low-density lipoprotein (VLDL), and decreases lipoprotein lipase activity. A defective lipoprotein lipase activity leads to the decreased clearance of fasting and postprandial TG-rich lipoproteins and to the decreased production of HDL [1]. The elevated level of fasting and postprandial TG-rich lipoproteins is the central lipoprotein abnormality observed in the metabolic syndrome [1].

Diacylglycerol (DAG) oil is a natural oil that is present in edible vegetable oils. Recent studies have indicated that DAG is effective for fasting and postprandial hyperlipidemia and for obesity prevention [2]. Therefore, we will here discuss the therapeutic application of DAG for the metabolic syndrome.

Biochemical properties of DAG

DAG is a natural component of various edible oils (Table 1) [3,4]. DAG can be synthesized enzymatically with the reverse reaction of 1,3-specific lipase, and consists mainly of the 1,3-species due to the migration of the acyl group in an equilibrium reaction. The ratio of the 1,3-DAG to 1,2-DAG in DAG oil is approximately 7:3 (Fig. 1) [2].

The mechanism of improvements in postprandial hyperlipidemia by DAG ingestion

Dietary TAG oil is hydrolyzed by lipase to free fatty acids (FFA) and 2-monoacylglycerol in the small intestinal lumen, and these are absorbed by intestinal cells (Fig. 2). In intestinal cells, TG is re-synthesized from 2-monoacylglycerol and two FFA via the 2-monoacylglycerol pathway [5]. Monoacylglycerol acyltransferase (MGAT) and diacylglycerol acyltransferase (DGAT) work in the 2-monoacylglycerol pathway [6,7]. TG is incorporated into chylomicrons (CM) by microsomal triglyceride transfer protein (MTP), which are released into the intestinal lymph and poured into the bloodstream [8].

In the case of DAG oil, the metabolic pathways in the intestinal cells are different from TAG oil (Fig. 2). Dietary DAG oil is mainly in the form of 1,3-DAG.

1,3-DAG would be hydrolyzed to initially to 1-monoacylglycerol and then, to glycerol and FFA, which are absorbed into the intestinal cells [9]. TG cannot be synthesized from 1-monoacylglycerol via the 2-monoacylglycerol pathway in the intestinal cells, because 1-monoacylglycerol cannot be the substrate for both DGAT and MGAT [6,7]. TG could be synthesized via the glycerol-3-phosphate pathway, which is less active than the 2-monoacylglycerol pathway [10].

Thus, the main digestive product of DAG is 1-monoacylglycerol, which is poorly reesterified into TAG in the small intestinal mucosa, while the main product of TAG digestion is 2-monoacylglycerol, which is easily reesterified to form TAG and incorporated into CM [2]. Slower reacylation to TAG in small intestinal cells is supposed to be the underlying mechanism improving the postprandial hyperlipidemia by substitution of DAG for TAG ingestion.

Effects of DAG oil on lipid and glucose metabolism

In our previous study with healthy volunteers, serum TG and remnant-like lipoprotein particles-cholesterol (RLP-C) concentrations after DAG ingestion were significantly lower than those after TAG ingestion, and the incremental area under the curve (IAUC) of serum RLP-TG after DAG loading was significantly lower than after

TAG loading [11]. Tomonobu et al. also reported that postprandial TG, RLP-C, and CM-TG concentrations were significantly lower after DAG ingestion than after TAG ingestion, and the IAUCs of TG and RLP-C concentrations after DAG ingestion were significantly smaller than after TAG ingestion in healthy volunteers [12]. In our previous study with diabetic patients, DAG loading significantly suppressed increases in postprandial serum TG and RLP-C and RLP-TG levels as compared with TAG loading, and the IAUCs for these lipid levels with DAG loading were also significantly smaller than those with TAG loading [13]. Long-term DAG oil consumption has been reported to increase HDL-C, and to decrease fasting TG, total cholesterol, LDL-C, and hemoglobin A1c levels, compared with TAG consumption [14-17].

The apolipoprotein C-II is a cofactor of lipoprotein lipase (LPL), which hydrolyzes TG of CM and VLDL [18]. We have a therapeutic experience with DAG oil to a patient with apolipoprotein C-II deficiency, a rare autosomal recessively-inherited disease [19]. Serum TG was remarkably increased from hour 4 (4 hour after experimental oil ingestion) by TAG, and the increment by DAG was almost half of that by TAG at hours 4 and 6. Serum VLDL-cholesterol was decreased by DAG up to hour 6 after oil ingestion, while TAG increased VLDL-cholesterol continuously. Serum RLP-C was linearly elevated by TAG from hour 2 to 8, but the increment by DAG was modest.

Our study demonstrated that DAG ingestion suppressed postprandial increase in serum TG, and TG-rich lipoprotein-cholesterol in a subject with apolipoprotein C-II deficiency, suggesting that DAG decreases TG-rich lipoprotein independent of lipoprotein lipase.

DAG ameliorates fasting and postprandial TG-rich lipoproteins, the central lipoprotein abnormality observed in the metabolic syndrome, independent of lipoprotein lipase, which is functionally defective in the metabolic syndrome. DAG may be a promising therapeutic item to the metabolic syndrome.

The mechanism of anti-obesity by DAG ingestion

Compared with the TAG-containing meal, the DAG-containing meal tended to induce higher postprandial energy expenditure and significantly lower postprandial respiratory quotient, suggesting that the DAG-containing meal has high postprandial lipid oxidation activity and a potential effect on high diet-induced thermogenesis. An increase in postprandial energy expenditure is supposed to be one of the mechanisms underlying the antiobesity effect of DAG [20]. Upregulated mRNA expressions associated with fatty acid transport (fatty acid translocase and fatty acid binding protein), β -oxidation (acyl-CoA oxidase and medium-chain acyl-CoA dehydrogenase), and thermogenesis (uncoupling protein-2) in the small intestine by DAG may explain in part mechanisms

for increased postprandial energy expenditure [21,22].

Antiobesity effect of long-term consumption of dietary DAG

A long-term consumption of DAG decreased body fat, especially visceral fat, and decreased body weight in both overweight and normal Japanese people, and obese subjects in the United States, compared with TAG consumption [23,24,25].

Open-labeled long-term consumption study indicated that DAG decreased body weight compared with TAG consumption [14]. In several long-term studies, decrease in waist circumferences and skin fold thickness by DAG consumption were observed [15,16,25].

Thus, several long-term clinical trials have indicated that DAG consumption results in losses of body weight and body fat, in healthy non-obese and obese men and women. Therefore, DAG may be beneficial in preventing excess adiposity, which is the main cause of the metabolic syndrome.

Conclusion

Obesity resides upstream of the constituents of the metabolic syndrome such as hypertension, impaired glucose tolerance, atherogenic dyslipidemia including increased TG and decreased HDL-C independent of hypercholesterolemia. DAG oil consumption

has been reported to ameliorate the constituents of the metabolic syndrome such as visceral obesity, dyslipidemia, and impaired glucose metabolism, suggesting the usefulness of DAG oil for the management and prevention of the metabolic syndrome.

References

1. Ruotolo G, Howard BV: **Dyslipidemia of the metabolic syndrome.** *Curr Cardiol Rep* 2002, **4**:494-500.
2. Tada N: **Physiological actions of diacylglycerol outcome.** *Curr Opin Clin Nutr Metab Care* 2004, **7**:145-149.
3. Abdel-Nabey AA, Shehata Y, Ragab MH, Rossell JB: **Glycerides of cottonseed oils from Egyptian and other varieties.** *Riv Ital Sostanze Grasse* 1992, **69**:443-447.
4. D'alonzo RP, Kozarek WJ, Wade RL: **Glyceride composition of processed fats and oils as determined by glass capillary gas chromatography.** *J Am Oil Chem Soc* 1982, **59**:292-295.
5. Yang LY, Kuksis A: **Apparent convergence (at 2-monoacylglycerol level) of phosphatidic acid and 2-monoacylglycerol pathways of synthesis of chylomicron triacylglycerols.** *J Lipid Res* 1991, **32**:1173-1186.
6. Cao J, Lockwood J, Burn P, Shi Y: **Cloning and functional characterization of a**

- mouse intestinal acyl-CoA:monoacylglycerol acyltransferase, MGAT2.** *J Biol Chem* 2003, **278**:13860-13866.
7. Cheng D, Nelson TC, Chen J, Walker SG, Wardwell-Swanson J, Meegalla R, Taub R, Billheimer JT, Ramaker M, Feder JN: **Identification of acyl coenzyme A:monoacylglycerol acyltransferase 3, an intestinal specific enzyme implicated in dietary fat absorption.** *J Biol Chem* 2003, **278**:13611-13614.
 8. White DA, Bennett AJ, Billett MA, Salter AM: **The assembly of triacylglycerol-rich lipoproteins: an essential role for the microsomal triacylglycerol transfer protein.** *Br J Nutr* 1998, **80**:219-229.
 9. Watanabe H, Onizawa K, Taguchi H, Kobori M, Chiba H, Naito S, Matsuno N, Yasukawa T, Hattori M, Shimasaki H: **Nutritional characterization of diacylglycerols in rats (in Japanese).** *J Jpn Oil Chem Soc* 1997, **46**:301-307.
 10. Friedman HI, Nylund B: **Intestinal fat digestion, absorption, and transport.** *Am J Clin Nutr* 1980, **33**:1108-1139.
 11. Tada N, Watanabe H, Matsuo N, Tokimitsu I, Okazaki M: **Dynamics of postprandial remnant-like lipoprotein particles in serum after loading of diacylglycerols.** *Clin Chim Acta* 2001, **311**:109-117.
 12. Tomonobu K, Hase T, Tokimitsu I: **Dietary diacylglycerol in a typical meal**

- suppresses postprandial increases in serum lipid levels compared with dietary triacylglycerol.** *Nutrition* 2006, **22**:128-135.
13. Tada N, Shoji K, Takeshita M, Watanabe H, Yoshida H, Hase T, Matsuo N, Tokimitsu I: **Effects of diacylglycerol ingestion on postprandial hyperlipidemia in diabetes.** *Clin Chim Acta* 2005, **353**:87-94.
14. Yasukawa T, Yasunaga K: **Nutritional functions of dietary diacylglycerols.** *J Oleo Sci* 2001, **50**:427-432.
15. Katsuragi Y, Toi T, Yasukawa T: **Effects of dietary diacylglycerols on obesity and hyperlipidemia.** *J Jpn Hum Dry Dock* 1999, **14**:258-262.
16. Otsuki K, Mori K, Onodera Y: **Final report from two-year intervention using edible oil rich in diacylglycerol.** *44th Annual Meeting of the Japanese Society of Human Dry Dock*, Kyoto, Aug. 2003, 27-29.
17. Yamamoto K, Asakawa H, Tokunaga K, Watanabe H, Matsuo N, Tokimitsu I, Yagi N: **Long-term ingestion of dietary diacylglycerol lowers serum triacylglycerol in type II diabetic patients with hypertriglyceridemia.** *J Nutr* 2001, **131**:3204-3207.
18. Breckenridge WC, Alaupovic P, Cox DW, Little JA: **Apolipoprotein and lipoprotein concentrations in familial apolipoprotein C-II deficiency.** *Atherosclerosis* 1982, **44**:223-235.

19. Yanai H, Tada N, Yoshida H, Tomono Y: **Diacylglycerol oil for apolipoprotein C-II deficiency.** *QJM* 2007, **100**:247-248.
20. Saito S, Tomonobu K, Hase T, Tokimitsu I: **Effects of diacylglycerol on postprandial energy expenditure and respiratory quotient in healthy subjects.** *Nutrition* 2006, **22**:30-35.
21. Murase T, Nagasawa A, Suzuki J, Wakisaka T, Hase T, Tokimitsu I: **Dietary alpha-linolenic acid-rich diacylglycerols reduce body weight gain accompanying the stimulation of intestinal beta-oxidation and related gene expressions in C57BL/KsJ-db/db mice.** *J Nutr* 2002, **132**:3018-3022.
22. Murase T, Aoki M, Wakisaka T, Hase T, Tokimitsu I: **Anti-obesity effect of dietary diacylglycerol in C57BL/6J mice: dietary diacylglycerol stimulates intestinal lipid metabolism.** *J Lipid Res* 2002, **43**:1312-1319.
23. Maki KC, Davidson MH, Tsushima R, Matsuo N, Tokimitsu I, Umporowicz DM, Dicklin MR, Foster GS, Ingram KA, Anderson BD, Frost SD, Bell M: **Consumption of diacylglycerol oil as part of a reduced-energy diet enhances loss of body weight and fat in comparison with consumption of a triacylglycerol control oil.** *Am J Clin Nutr* 2002, **76**:1230-1236.
24. Nagao T, Watanabe H, Goto N, Onizawa K, Taguchi H, Matsuo N, Yasukawa T,

Tsushima R, Shimasaki H, Itakura H: **Dietary diacylglycerol suppresses accumulation of body fat compared to triacylglycerol in men in a double-blind controlled trial.** *J Nutr* 2000, **130**:792-797.

25. Koyama W: **Long-term effects of diacylglycerol used as libitum as cooking oil in home.** *24th Annual Meeting of Japan Society for the Study of Obesity*, Chiba, Nov. 2003, 13-14.

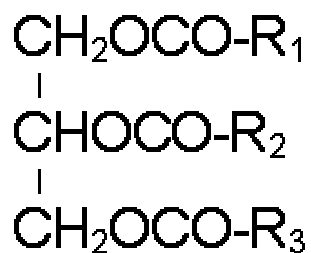
(figure legends)

Fig. 1. Structure of triacylglycerol and diacylglycerol. R1, R2, and R3 indicate fatty acids.

Fig. 2. Digestion and absorption of triacylglycerol. DGAT, diacylglycerol acyltransferase; FFA, free fatty acids; MAG, monoacylglycerol; MGAT, monoacylglycerol acyltransferase; MTP, microsomal triglyceride transfer protein; TAG, triacylglycerol.

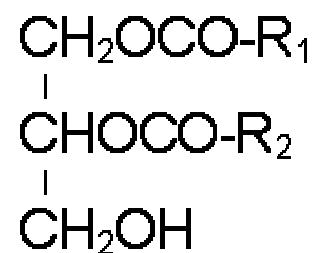
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A. Triacylglycerol (TAG)

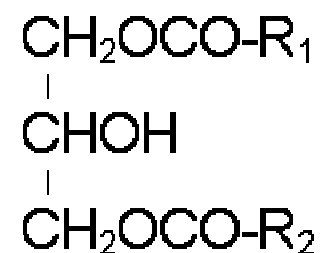


B. Diacylglycerol (DAG)

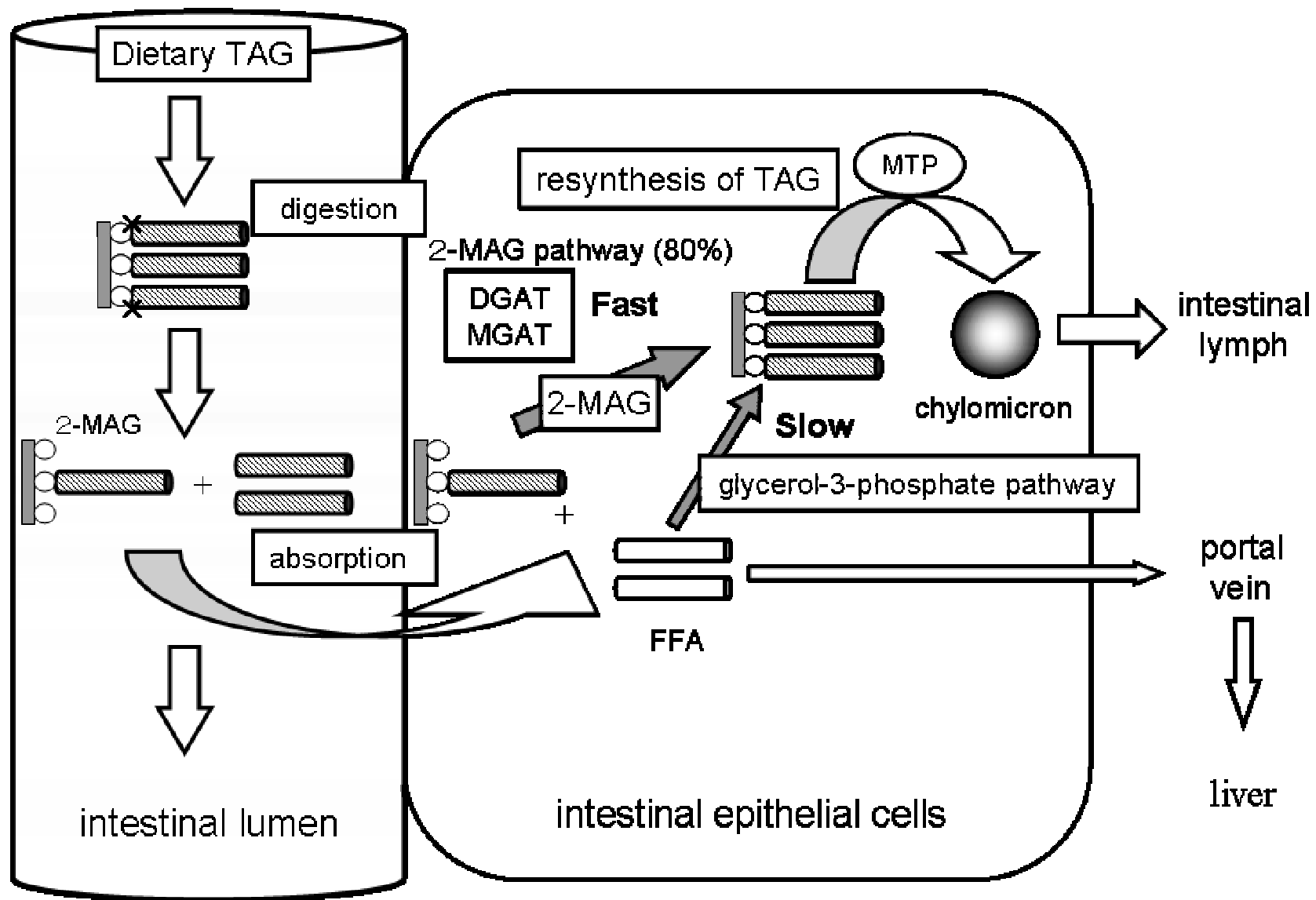
a) 1,2-DAG

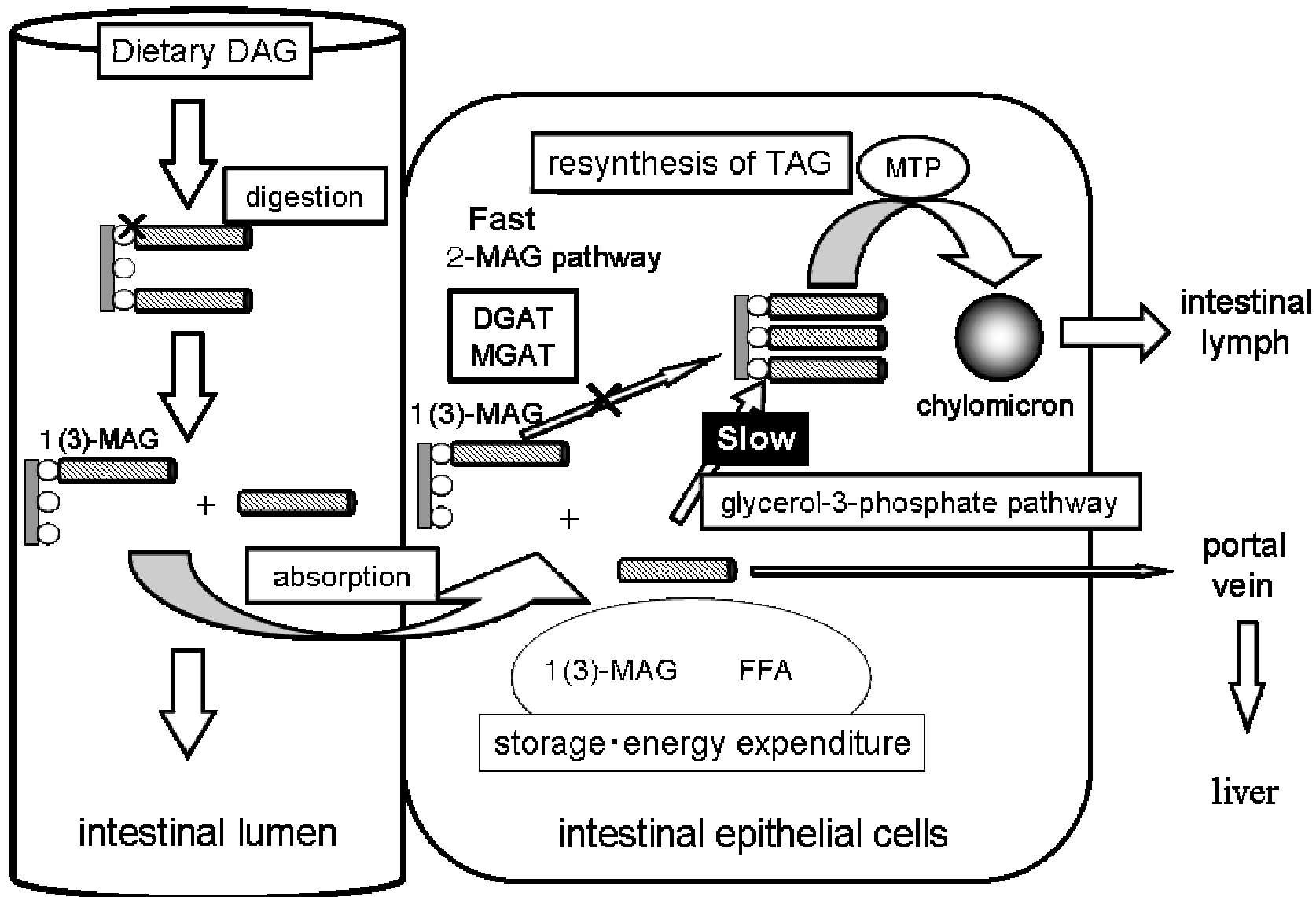


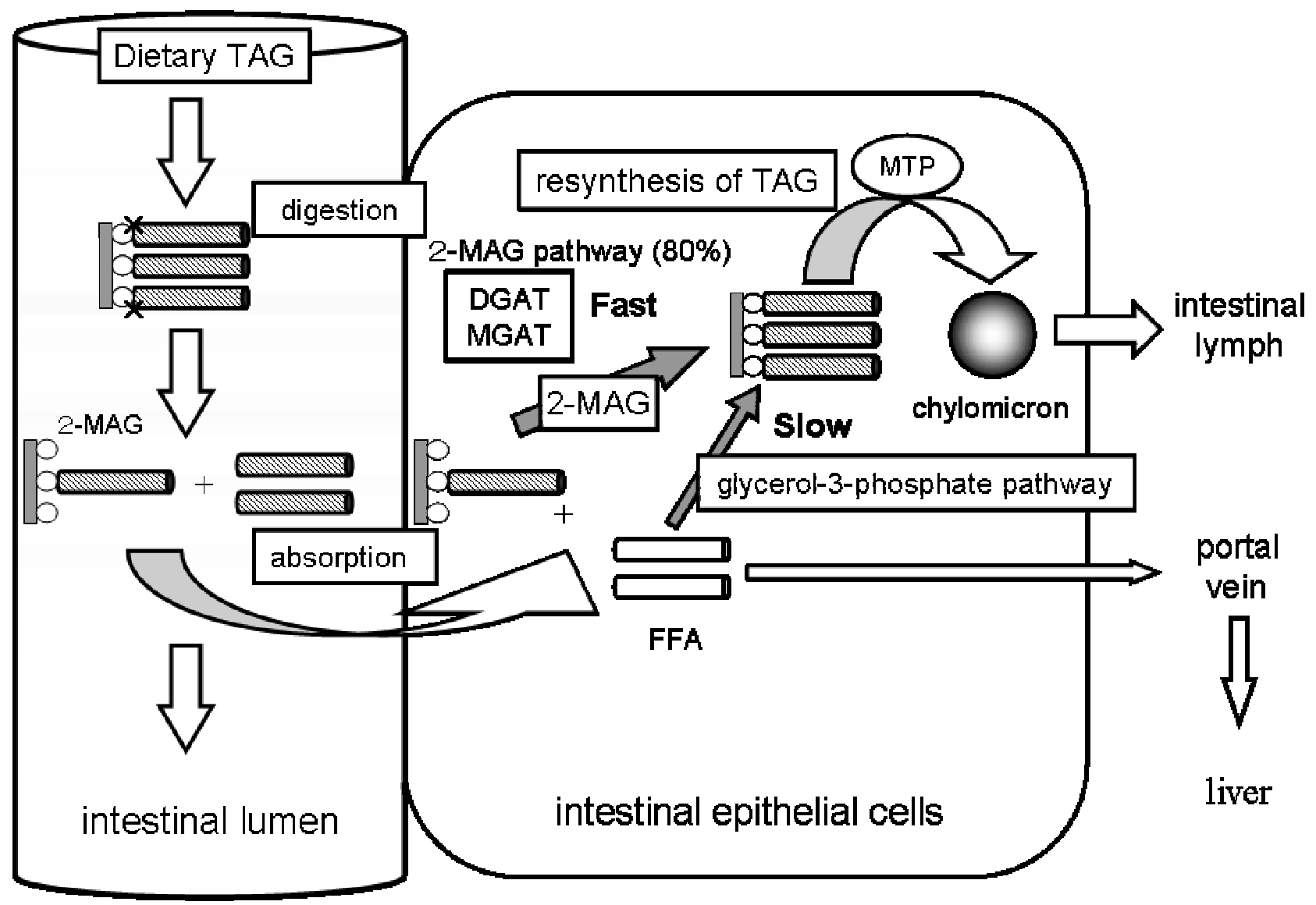
b) 1,3-DAG

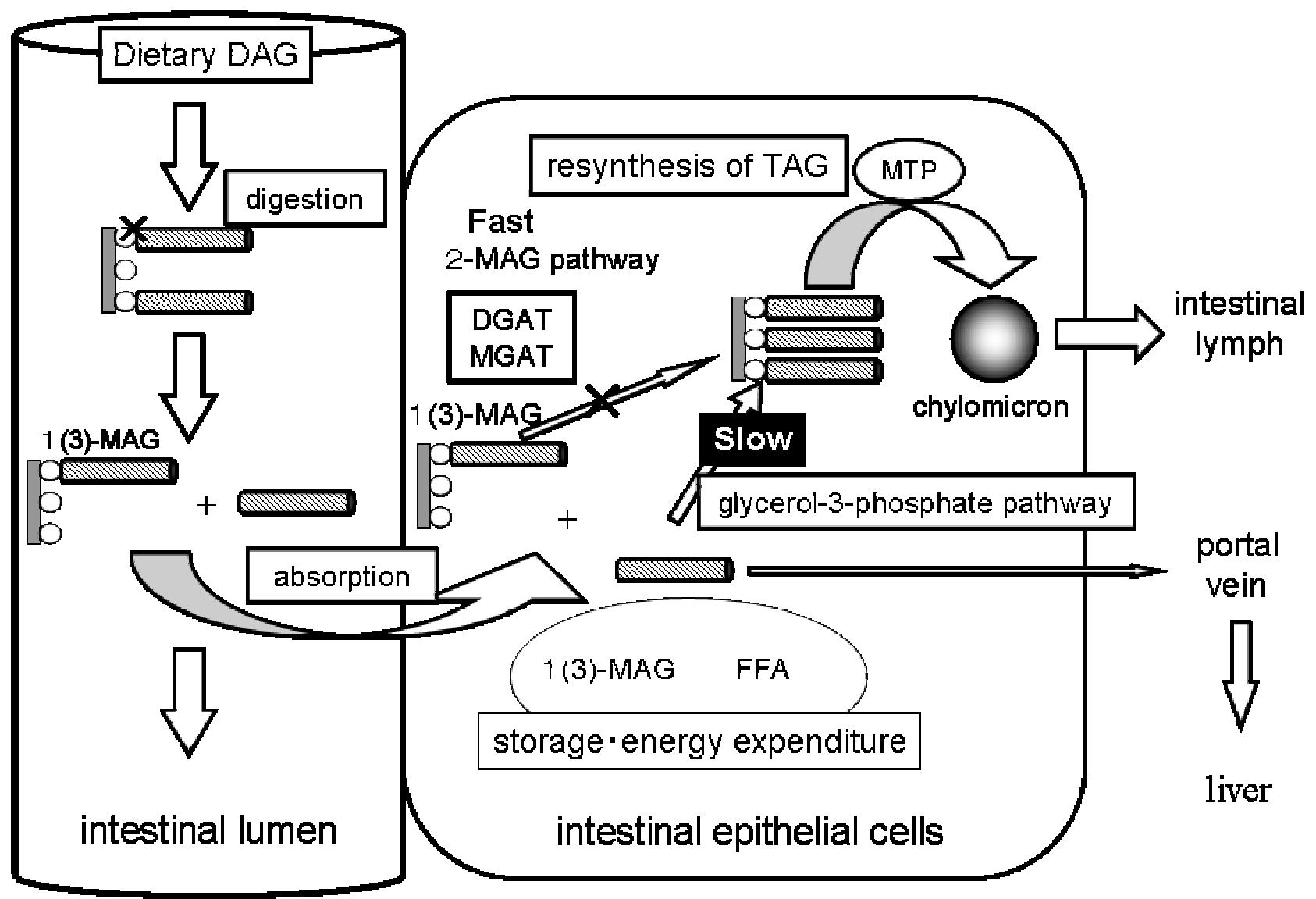


$$1,2\text{-DAG} : 1,3\text{-DAG} = 3 : 7$$









Additional files provided with this submission:

Additional file 1: table 1,2,3.doc, 49K

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