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Review

Postprandial metabolism of meal triglyceride in humans☆,☆☆

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ABSTRACT

The intake of dietary fat above energy needs has contributed to the growing rates of obesity worldwide. The concept of disease development occurring in the fed state now has much support and dysregulation of substrate flux may occur due to poor handling of dietary fat in the immediate postprandial period. The present paper will review recent observations implicating cephalic phase events in the control of enterocyte lipid transport, the impact of varying the composition of meals on subsequent fat metabolism, and the means by which dietary lipid carried in chylomicrons can lead to elevated postprandial non-esterified fatty acid concentrations. This discussion is followed by an evaluation of the data on quantitative meal fat oxidation at the whole body level and an examination of dietary fat clearance to peripheral tissues — with particular attention paid to skeletal muscle and liver given the role of ectopic lipid deposition in insulin resistance. Estimates derived from data of dietary-TG clearance show good agreement with clearance to the liver equaling 8–12% of meal fat in lean subjects and this number appears higher (10–16%) in subjects with diabetes and fatty liver disease. Finally, we discuss new methods with which to study dietary fatty acid partitioning in vivo. Future research is needed to include a more comprehensive understanding of 1) the potential for differential oxidation of saturated versus unsaturated fatty acids which might lead to meaningful energy deficit and whether this parameter varies based on insulin sensitivity, 2) whether compartmentalization exists for diet-derived fatty acids within tissues vs. intracellular pools, and 3) the role of reduced peripheral fatty acid clearance in the development of fatty liver disease. Further advancements in the quantitation of dietary fat absorption and disposal will be central to the development of therapies designed to treat diet-induced obesity. This article is part of a Special Issue entitled Triglyceride Metabolism and Disease.

1. Introduction

Traditionally, cardiovascular disease risk factors have been determined and measured in the fasting state. However in recent years there has been an increasing awareness on the importance of fed-state events in the development and exacerbation of disease. Epidemiological studies have demonstrated that the presence of postprandial hypertriglyceridemia poses an independent risk for coronary atherosclerosis [1–7]. Furthermore, the efficiency with which the body manages incoming dietary lipid can modulate disease risk in other chronic conditions such as obesity [8], type 2 diabetes [9,10], and non-alcoholic fatty liver disease, NAFLD [11]. Indeed, if poor metabolism of dietary triglyceride (TG) leads to ectopic lipid deposition, postprandial events may contribute more to disease development than currently appreciated. The goal of the present paper is to review current knowledge on the absorption and metabolic fate of dietary-TG in humans. Beginning with recent observations of a delay in the complete absorption of meal-TG, the paper will describe the fates of chylomicron fatty acids, from clearance into adipose and skeletal muscle, to the latest data on the contribution of dietary-TG to the development of NAFLD. A better understanding of the process of dietary-TG partitioning is central to the future development of therapies designed to improve dietary fat handling. The long history of excellent papers published in this research area precludes mention of all significant work; we have focused on recent studies and highlighted technical developments that are supporting the rapidly expanding knowledge in this field.

2. Absorption of dietary fat

2.1. Intestinal metabolism and chylomicron clearance

As shown in Fig. 1A, dietary fat absorbed into the enterocyte can be 1) repackaged into chylomicron (CM) lipoprotein particles for

Abbreviations: CE, cholesterol ester; CM, chylomicrons; ^{18}FTHA, [^{18}F]fluoro-6-thia-heptadecanoic acid; NAFLD, non-alcoholic fatty liver disease; LPL, lipoprotein lipase; MUFA, monounsaturated fatty acids; NEFA, non-esterified fatty acids; PET/CT, positron emission tomography and computed tomography; PL, phospholipid; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TG, triglycerides; VLDL, very low-density lipoprotein

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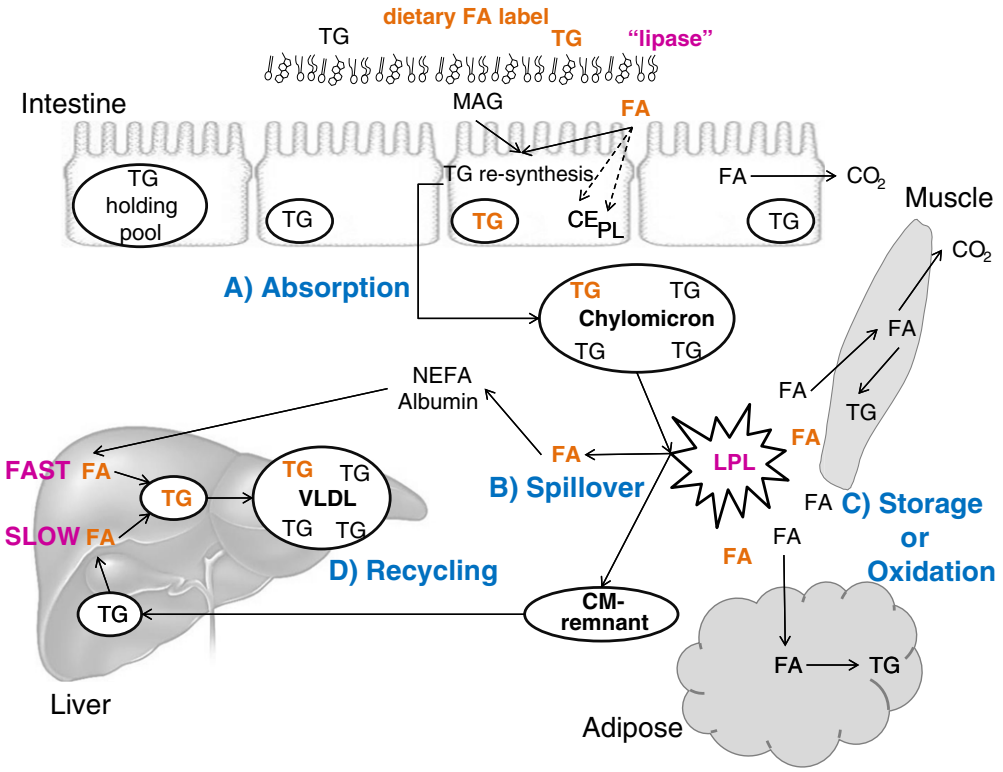

Fig. 1. Meal TG absorption and metabolism.After eating a meal, dietary fat (triglyceride, TG) is hydrolyzed by lipase to yield fatty acids (FA) and monoacylglycerol (MAG) which are then absorbed (A) into the enterocyte. Within the enterocyte, FA have several fates: 1) partitioning into cholesteryl ester (CE) or phospholipid (PL), 2) oxidation, or reesterification to form TG for 3) incorporation into chylomicrons (CM) or 4) storage in an intracellular TG storage or holding pool. Chylomicron-TG is metabolized at the tissue level by lipoprotein lipase (LPL), which hydrolyzes CM-TG to release FA for tissue uptake. Some of these released FA will not be taken up by tissues but will rather "spillover" (B) into the plasma non-esterified fatty acid (NEFA) pool and can then be taken up by the liver or other tissues. Within the major tissues (muscle or adipose), dietary-derived FA can be stored or oxidized (C) depending on tissue needs. After hydrolysis of chylomicron-TG the particle becomes smaller, forming a CM-remnant. This remnant particle is taken up by the liver and the TG remaining in the particle can be repackaged into VLDL (D) thereby recycling the dietary FA. This pathway is relatively slower for incorporation into VLDL-TG compared to the incorporation of FA from the plasma free fatty acid pool, which occurs rapidly.

distribution to the body tissues, 2) stored within the enterocyte in a lipid droplet or TG storage pool, 3) partitioned into other lipids including cholesteryl ester (CE) or phospholipid (PL), and 4) oxidized. Incorporation of dietary fatty acids into TG or other lipids within the enterocyte may depend on chain length and structure (saturation). For example, myristate is preferentially packaged into TG (over 95%), whereas a portion of palmitate is incorporated into PL (18%) and CE (7%) [12]. Stearate appears better incorporated into PL (estimated 33%) compared to palmitate, and less ends up in TG and CE [12,13]. Polyunsaturated fatty acids (PUFA) including 18:2n6 and 18:3n3 are also proportionally incorporated more into CE and PL compared to 16:0 and 18:1 [14,15]. Since the majority of dietary fatty acids are processed as CM-TG, the fate of this lipid fraction will be the focus of the remaining portion of this review.

Over the past 10 years, two striking characteristics of enterocyte-TG processing have emerged — 1) that lipids secreted at the very onset of a meal are those that were consumed in an earlier meal, suggesting the presence of an enterocyte storage pool for TG, and 2) a cephalic phase release of CM tied to oral stimulation by food intake. The first phenomenon noted is an early rise in blood-TG concentrations within minutes of the consumption of a meal containing fat [16]. This rise in TG occurring 10–30 min after the onset of the meal is denoted "the early peak" to delineate it from the primary postprandial peak of blood TG which occurs 3–4 h after meal initiation. The timing of the early peak observed in the blood occurs before the absorption of the meal fat into the enterocyte could have occurred [17] and is more likely to occur when the previous evening meal was high in fat [17,18]. We have recently shown via utilization of stable isotopes that 10–12% of TG consumed in the previous evening meal appears in new CM, first occuring 15–20 min after the onset of morning food consumption. This observation indicates that the timing of meal-TG storage in the intra-enterocyte pool can extend to at least 16 h [18] and supports a taste for fat. The second phenomenon is connected to the overall cephalic phase response [19–22]. The early meal-induced rise in CM-TG concentration can occur when fat is only tasted and not consumed [23], and also when only glucose is consumed [24]. The existence of an oral taste sensor for lipids is intriguing and has led to the generation of hypotheses on a taste–gut–brain axis which is currently an active area of investigation [25].

Potential questions arising from these findings:

1) Does the pre-release of CM-TG before influx of meal fat provide some physiological benefit? Fat-sensitive hormone release may "prime" the body by stimulating upregulation of lipolytic enzymes and fatty acid transport proteins in preparation for the incoming lipid load.
2) Does glucose-induced release of CM-TG also occur with other sweet tastes (i.e. fructose or artificial sweeteners)? This would have implications for individuals who rely on artificially-sweetened foods and may already have impairments in postprandial lipid metabolism.

2.2. The second meal effect

Plasma concentrations of TG rise progressively over the day due to repeated consumption of fat-containing meals. Peak TG levels occur between midnight and 2 AM [26,27]. This change in plasma-TG is a result of increases in both CM particles and TG content [28]. After a