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Review

Regulation of chylomicron production in humans ☆

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ABSTRACT

Chylomicrons (CM), secreted by the intestine in response to fat ingestion and to a lesser extent during the postabsorptive state (lipid poor CM), are the major vehicles whereby ingested lipids are transported to and partitioned in energy-storing and energy-utilizing tissues of the body. CM contribute significantly, although not exclusively, to postprandial lipemia. Intestinal CM production is upregulated in humans under conditions of insulin resistance and CM overproduction in such conditions contributes to the highly prevalent dyslipidemia of these conditions. In addition, CM remnants possess direct atherogenic properties. CM assembly and secretion is regulated by many factors apart from ingested fat (the primary stimulus for their secretion), including a number of nutritional, hormonal, metabolic and genetic factors. Understanding the mechanisms that regulate CM production in health and disease may lead to treatments and prevention of atherosclerosis and cardiovascular disease. This review aims to summarize current understanding of CM production in humans. This article is part of a Special Issue entitled Triglyceride Metabolism and Disease.

1. Introduction

1.1. Postprandial lipemia and atherosclerotic cardiovascular risk

Postprandial lipemia, which may be more pronounced in conditions in which there is either overproduction of lipoprotein particles or delayed clearance of those particles from the circulation, is increasingly recognized as a prominent feature of obesity, insulin resistance, type 2 diabetes (T2D) and cardiovascular disease (CVD) [11,24,33,127,152], as well as occurring as a result of rarer monogenic conditions such as heterozygous deficiency of lipoprotein lipase (LPL) [13]. Recent studies have indicated non-fasting plasma triglycerides (TG) as a strong predicator of cardiovascular events [6,135]. Although postprandial TG also includes a prominent contribution from hepatic very-low density lipoprotein (VLDL), intestinal chylomicron (CM) is the predominant contributor [33]. Aside from contributing to postprandial lipemia, CM remnants, the degradation products of CM following their lipolysis by LPL, are linked to CVD [24,32,78,92,177,186]. CM may directly contribute to atherosclerosis, thus CM remnant particles can rapidly penetrate the arterial wall and are preferentially retained in the arterial vessel [157–159]. Mounting evidence supports the notion that atherosclerosis is in part a consequence of disordered CM metabolism. Therefore, there is increasing interest in characterizing CM metabolism [176] and more closely examining the role of CM and their remnants in CVD [30]. Potential strategies to optimize CM metabolism in order to reduce postprandial lipemia and the accumulation of CM remnants include inhibition of lipid absorption, inhibition of intestinal CM synthesis and secretion, and enhancement of CM and CM remnant clearance from the circulation.

2. Chylomicron metabolism: a brief overview

CM particles are synthesized in intestinal enterocytes. A truncated form of apolipoprotein (apo) B, apoB-48, is formed by posttranscriptional mRNA editing of *APOB* in intestinal enterocytes. Editing changes codon 2153 in the middle of the apoB-100 coding region from CAA, coding for glutamine, to UAA, a translation stop signal [156]. ApoB-48 is lipidated with neutral lipids to form primordial CM particles, a process facilitated by microsomal triglyceride transfer protein (MTP) [79,198]. Inadequately lipidated apoB-48 protein may direct it to degradation. However, in contrast to VLDL secretion in hepatocytes, apoB-48 degradation in the enterocytes does not represent a major regulatory mechanism since the enterocytes are capable of secreting apoB-48 as a high-density lipoprotein in lipid-poor state [64]. It is important to make the distinction of particle numbers from particle size, since increased particle numbers lead to increased CM remnant numbers, hence potentially increased atherosclerotic risk, whereas increased particle size leads to greater lipid loading of an unchanged number of CM particles. Dietary lipid transport following a meal has been generally believed to be through dramatically increased CM particle size, i.e. increased amount of neutral lipid per particle, with a relatively lesser increase in particle numbers [31].

Abbreviations: apo, apolipoprotein; CM, chylomicron; CVD, cardiovascular disease; FFA, free fatty acids; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; HL, hepatic lipase; LPL, lipoprotein lipase; MTP, microsomal triglyceride transfer protein; T1D, type 1 diabetes; T2D, type 2 diabetes; TG, triglycerides; VLDL, very-low density lipoprotein

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CM particles are secreted into the intestinal lymph and released into the circulation through the thoracic duct. Detailed description of lipid absorption and CM synthesis in the intestine has been reviewed recently elsewhere [79,80,86]. After entering the circulation, CM interact with other lipoprotein fractions and exchange apolipoproteins other than apoB-48, including acquiring apoC-II, which mediates hydrolysis of CM particles by LPL, and apoC-III, which inhibits LPL. The majority of the fatty acids released by hydrolysis of CM are taken up by tissues (e.g. adipose tissue, liver and muscle). The hydrolysis of CM particles results in significantly reduced particle size, with transfer of phospholipids to HDL and movement of unesterified cholesterol from the core to the surface of the particle. Binding of CM remnant surface apoE to cell surface receptors represents the major pathway of CM remnant catabolism in the liver [34]. CM remnant clearance is greatly reduced in apoE2/2 homozygotes [166]. On the other hand, apoE2/2 patients have severe atherosclerosis, suggesting apoE is not required for CM remnant uptake by the vessel wall [12].

Since there is only one non-exchangeable apoB-48 per CM particle [153], since apoB-48 is uniquely present only in intestinally-derived CM and not in hepatically-derived VLDL in humans, and since the apoB-48 molecule remains an integral part of the CM remnant particle following lipolysis of the CM, apoB-48 can be utilized *in vivo* to track the secretion and metabolic fate of intestinally-derived CM particles. Using stable isotope labeling and multicompartmental modeling approach, we and others have investigated apoB-48 kinetics in healthy and dyslipidemic individuals under various conditions. Since apoB-48 concentration in the circulation is too low to assess stable isotope enrichment in the postabsorptive state, such studies are usually performed under conditions of repetitive, frequent food ingestion. A summary of kinetics studies of apoB-48 metabolism in humans is presented in Table 1. To reflect the focus of this topic, only apoB-48 metabolism-related findings are outlined. These studies have demonstrated the usefulness of this approach in dissecting the mechanism of CM metabolism non-invasively *in vivo* under a variety of metabolic conditions (i.e. health and diseases). Also using this approach, many factors (metabolic, hormonal, genetic and pharmacological) affecting CM metabolism have been identified, which are discussed in greater detail below.

3. CM metabolism in disease states

Several disorders are associated with abnormalities of CM metabolism. CM retention disease is an inherited disorder that affects the absorption of dietary fats, cholesterol, and certain fat-soluble vitamins. Mutations in the SAR1B gene encoding Sar1 GTPase impair transportation of CM within enterocytes and subsequent release of CM into the bloodstream [148]. In heterozygous familial hypercholesterolemia, apoB-48 and remnant-like particle-cholesterol are elevated [41]. CM

Table 1
Kinetics studies of CM apoB-48 metabolism in humans using endogenous labeling with stable isotopes.

Subjects	Experimental design/interventions	Findings	Ref
Healthy	[$^{13}C_6$]phenylanine labeling 14-day sampling monoexponential analysis	Lower tracer enrichment and longer residence time for apoB-48 than for apoB-100	[84]
Healthy		Lower tracer enrichment and longer residence time for apoB-48 than for apoB-100 Greater FCR for apoB-48 than for apoA-I in TRL	[188]
Healthy		Similar FCRs for TRL apoB-48 and VLDL apoB-100 in the fed state Correlation of TRL apoB-48 PS with TRL apoB-48 PR Correlation of VLDL apoB-100 PS with both PR and FCR of VLDL apoB-100 and PR of TRL apoB-48	[194]
Healthy	apoE3/E3 and apoE3/E4 genotypes	Similar CM remnant clearance in apoE3/E3 and apoE3/E4 subjects	[196]
Healthy	Monoexponential analysis	Similar TRL-apoB100 and apoB-48 FCRs Lower apoB-48 tracer enrichment than apoB-100	[110]
Healthy		Delayed CM remnant FCR associated with enhanced apoA-I FCR	[195]
Healthy	Broad range of HOMA-IR	Increased TRL-apoB-48 PR in hyperinsulinemia (insulin resistance)	[47]
Healthy	IH infusion	Increased TRL-apoB-48 PR with elevated circulating FFA	[49]
Healthy	Treated with rosiglitazone/placebo	Improved insulin sensitivity, increased TRL-apoB-48 with tendency to increase PR and decrease FCR of TRL-apoB-48 by rosiglitazone	[48]
Healthy	Euglycemic clamps with hyperinsulinemia or normoinsulinemia, IH infusion	Acute suppression of VLDL-apoB-48 production, by insulin, partly through insulin suppression of circulating FFA	[145]
Healthy	Pancreatic clamp with basal or high glucagon infusion	Insignificant effects of glucagon on VLDL-apoB-48 metabolism in the fed state	[201]
Healthy	Multiple lipoprotein fractions	Similar clearance pattern and competition between apoB-48 and apoB-100	[205]
T2D	Euglycemic/hyperglycemic-hyperinsulinemic clamp, IH infusion	Blunted acute insulin suppression of intestinal lipoprotein production in T2D	[134]
T2D+HTG	Treated with fenofibrate/atovarstatin	Improvement of apoB-48 metabolism by fenofibrate and atorvastatin via different mechanisms: fenofibrate increased FCR, atovastatin decreased PR	[72]
T2D Healthy		Increased production and impaired clearance of TRL-apoB-48 in T2D	[73]
FH Healthy		Increased apoB-48 in heterozygous FH with the same null LDL-R gene due to higher PR but not lower FCR	[184]
CKD, obesity, MS		Decreased TRL clearance in CKD	[8]
apoE- deficiency Healthy	[$^{13}C_6$]phenylanine labeling	Delayed VLDL-apoB-48 catabolism in homozygous apoE deficiency	[83]
CHL	Treated with extended-release niacin/niacin+ lovastatin/placebo	Increased TRL-apoB-48 FCR by niacin	[99]
Moderate primary HC	Treated with ezetimibe	No significant effect TRL apoB-48 metabolism by ezetimibe	[182]
Hyperlipidemic	Treated with ezetimibe, simvastatin, alone or in combination	Combination therapy decreased TRL-apoB-48 through increased PR	[183]
Dysb+FH	Treated with fenofibrate	Elevated TRL-apoB-48 FH+/dysb+ subjects due to lower clearance Increased TRL-apoB-48 clearance with fenofibrate treatment in FH+/dysb+ subjects	[185]

Notes: Studied were performed at constantly fed state, with frequent ingestions of small portion meals, and with primed constant infusion of deuterated leucine as tracer and multicompartmental modeling, unless otherwise stated. Abbreviations used: CHL, combined hyperlipidemia; CKD, chronic kidney disease; dysb, dysbetalipoproteinemia; FCR, fractional catabolic rate; FH, familial hypercholesterolemia; HC, hypercholesterolemia; HTG, hypertriglyceridemia; HOMA-IR, homeostatic model assessment of insulin resistance; IH, Intralipid plus heparin; MS, metabolic syndrome; PR, production rate; T2D, type 2 diabetic patients.