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Review

Pathophysiology of hypertriglyceridemia ☆

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ABSTRACT

The importance of triglycerides as risk factor for CVD is currently under debate. The international guidelines do not include TG into their risk calculator despite the recent observations that plasma TG is an independent risk factor for CVD. The understanding of the pathophysiology of triglycerides opens up avenues for development of new drug targets. Hypertriglyceridemia occurs through 1. Abnormalities in hepatic VLDL production, and intestinal chylomicron synthesis 2. Dysfunctional LPL-mediated lipolysis or 3. Impaired remnant clearance. The current review will discuss new aspects in lipolysis by discussing the role of GPIHBP1 and the involvement of apolipoproteins and in the process of hepatic remnant clearance with a focus upon the role of heparin sulfate proteoglycans. Finally we will shortly discuss future perspectives for novel therapies aiming at improving triglyceride homeostasis. This article is part of a Special Issue entitled Triglyceride Metabolism and Disease.

1. Introduction

Lipoproteins are large macromolecular complexes of hydrophobic lipids and proteins designed to transport water insoluble lipids such as triglycerides and cholesteryl esters in body fluids [1]. Lipoproteins contain a hydrophobic core of triglycerides and cholesterol ester enveloped by a monolayer of phospholipids, unesterified cholesterol and apolipoproteins. Triglyceride-rich lipoproteins (TRLs) originate from the intestine (chylomicrons) or from the liver (very-low-density lipoproteins, VLDL). After ingestion of a meal triglycerides are taken up in the enterocytes and packaged into large particles containing apoB48 as core protein. Upon secretion into the lymphatic system remodeling occurs before chylomicron remnants enter the systemic circulation [2]. Endogenous synthesized TG in the liver is packaged into very low density lipoproteins (VLDL) containing apoB100 as core protein. TRLs play an essential role in delivering fatty acids (FFA) to tissues as source of energy (heart and skeletal muscle) or for storage (adipose tissue). Plasma TG levels are determined by several key metabolic pathways: Intestinal uptake from dietary fat, hepatic production, peripheral lipolysis induced TRL remodeling and hepatic removal of VLDL and chylomicron remnants will be discussed [3]. Abnormalities in TG metabolism are a hallmark of a number of clinical disturbances including type 2 diabetes, familial combined hyperlipidemia, dysbetalipoproteinemia and severe hypertriglyceridemia and are conferred to increased risk for CVD.

Recently, a scientific statement from the American Heart Association was issued to highlight the notion that plasma TG levels display a steady increase which contributes in a large extent to the continuously increasing cardiometabolic risk particularly [4].

In the present review, recent insight into pathophysiology of hypertriglyceridemia and future developments in triglyceride-lowering therapies are discussed.

2. TG metabolism (Fig. 1)

2.1. Dietary fat absorption and formation of chylomicrons in the intestine

Triglycerides derived from dietary sources are hydrolysed in the intestine by pancreatic lipase in 2-monoacylglycerol (2-MG) and fatty acid (FA), which can be absorbed by the enterocytes by diffusion or specific transporters such as FAT/CD36 [5]. Within the enterocyte, 2-MG and FA are resynthesized into TGs by the enzyme acyl-CoA:diacylglycerol acyltransferase (DGAT) [6]. Subsequently, microsomal triglyceride transfer protein (MTP) in complex with protein disulphite isomerase (PDI) facilitates the lipidation of apolipoprotein B48 (apoB48), as a first step towards chylomicron formation. Epithelial COPII (Coatomere Protein II) transport carriers like SAR1a and SAR1b are essential for the transport of chylomicrons to the Golgi apparatus [7]. Human relevance is underscored by the observation that chylomicron retention disease and Anderson disease are autosomal recessive disorders of severe fat malabsorption with a complete absence of circulating apoB48 particles due to a genetic defect in the COPII machinery

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[8]. Nascent chylomicron particles are exocytosed from the basolateral membrane and enter the lymphatic compartment and eventually the systemic circulation [5]. The intestine harbors the option to synthesize apoC-III and possibly apoA-V. Whether these apolipoproteins are secreted associated with chylomicron particles is still unknown. Upon entering the circulation direct apolipoprotein exchange occurs with HDL particles enriching the chylomicron particles with apoE and apoC-III. In the fasting state chylomicrons are small, whereas ingestion of a meal leads to an increase of chylomicron size rather than chylomicron particle number.

2.2. Hepatic VLDL production

TG is synthesized in the liver and packaged into VLDL particles, with apoB100 as the main protein. The required fatty acids are derived from de novo synthesis using glucose as substrate (DNL) or

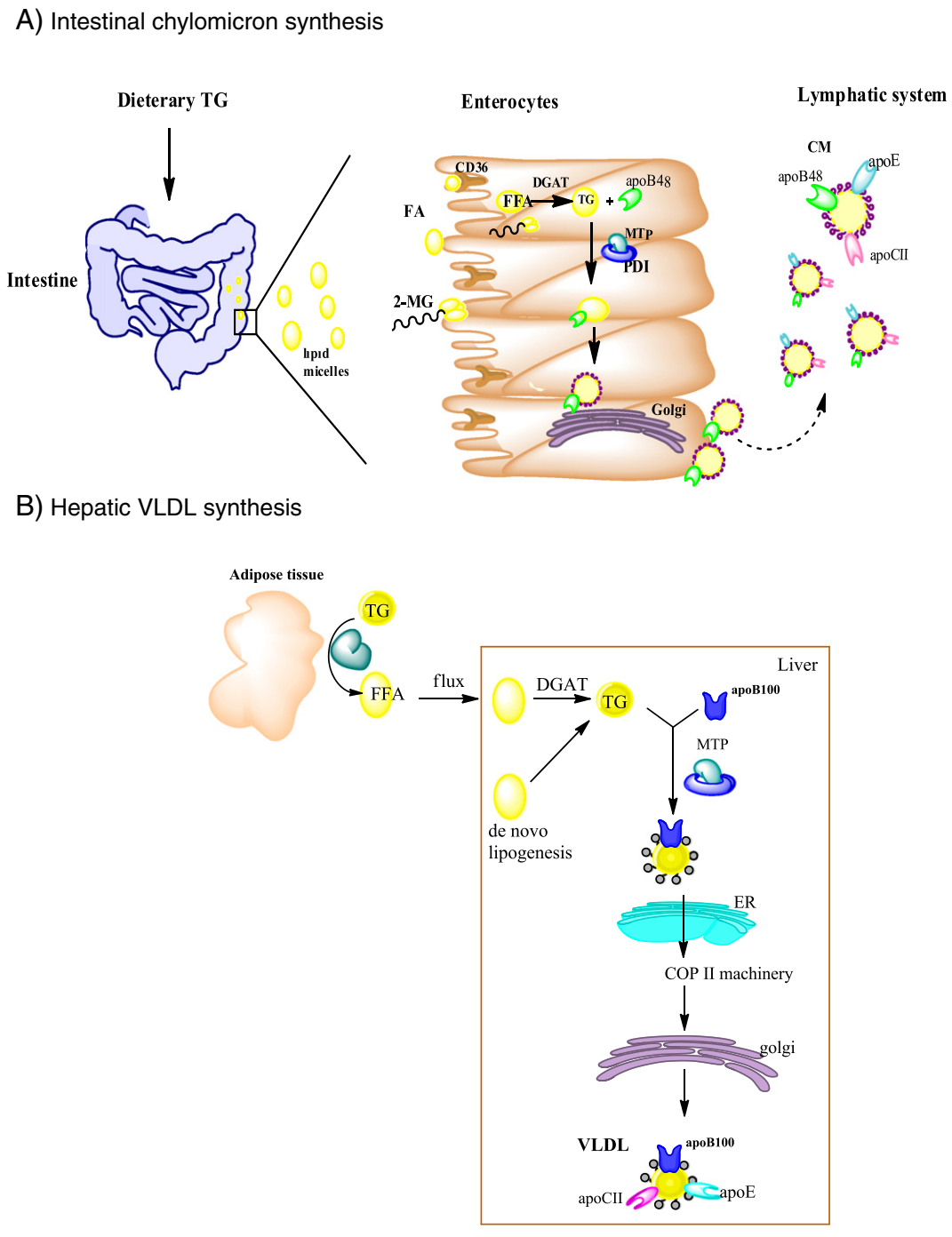

Fig. 1. TG metabolism. A. Intestinal chylomicron and hepatic VLDL synthesis. 1. Dietary lipids are taken up in the enterocytes, incorporated into chylomicron particles that are secreted into the lymphatic system. DGAT, the COPII machinery system and MTP are required for the intracellular processing of chylomicrons. 2. Hepatic VLDL synthesis involved a series of intracellular processes enabling the formation of lipid-enriched apoB100 particles that can be excreted. B. Peripheral Lipolysis. GPIHBP1 is involved in the transport of LPL through the endothelial cell layer to the cell surface and is required for stabilization of LPL. At the endothelial cell surface GPIHBP1 forms the platform to allow TG hydrolysis. C. Hepatic TRL clearance. TRL clearance involves 3 hepatic receptors: LDLr, LRP1 and HSPG. Sulf2 is an extracellular protein that modulates HSPG thereby influencing hepatic TRL clearance.