12.1. INTRODUCTION

Maintaining normal physiological homeostasis depends upon a coordinated metabolism of both water-soluble and insoluble substrates. In humans the body derives these molecules — such as glucose, amino acids, and fatty acids — from complex food matter. Water-soluble substrates can circulate readily in blood, while water-insoluble molecules — such as fatty acid, triacylglycerol, and cholesterol — require amphipathic carriers to transport them from the site of biosynthesis (liver and intestine) to the target tissue. For fatty acid, albumin serves as the major transporter. For triacylglycerol and cholesterol, however, macromolecular complexes aggregate the hydrophobic molecules into the core and cover the surface with amphipathic proteins and phospholipids to solubilize the particles in the lymphatic and circulatory systems. These macromolecules belong to a class of proteins, plasma lipoproteins, with specific functions and cellular targets. In the clinic these lipoproteins prognosticate the risk of cardiovascular disease (CVD).

Lipoproteins divide usually into five major types: chylomicron, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Each lipoprotein type exhibits characteristic density, size, and composition. As implied in the name, the density varies from the low-density chylomicron (<0.95 g/ml) to the high-density HDL (1.2 g/ml). Size also varies. The chylomicron has the...
largest diameter (75–1,200 nm), and HDL has the smallest (5–12 nm). The physical property variation arises from each lipoprotein’s distinct composition. In a chylomicron, cholesterol, triacylglycerol, and phospholipid predominate and constitute about 90% of the particle. Protein constitutes only about 10%. In contrast, the smaller HDL has less cholesterol, triacylglycerol, and phospholipid (65% of the particle) but more protein (over 30%).

Even though lipoproteins contain a high fraction of triacylglycerol and cholesterol, these hydrophobic molecules do not determine the physiological function. Instead, function depends heavily upon the action of the associated proteins. Each lipoprotein contains a unique set of apoproteins or apolipoproteins. (Proteins separated from a lipid–protein complex have the designation of apoproteins, derived from the contraction of the two terms “apodized protein”). In LDL, apoB-100 (apolipoprotein B-100) predominates, whereas in HDL apoA-I (apolipoprotein A1) predominates. Indeed, these markedly different proteins, apoB-100 (513 kD, (kilodalton)) and apoA-I (29 kD), confer lipoprotein targeting and functional specificity [1,2].

12.2. CHYLOMICRONS AND TRIACYLGlycerOL

The function of chylomicron and LDL illustrates the distinct physiological roles. Chylomicrons play a major role in transporting triacylglycerol from the intestine after a meal. Normal plasma lipid, cholesterol, and triacylglycerol levels range from 3.6–6.8, 1.3–2.6, and 0.8–2.4 g/l, respectively [2]. In the postprandial state, triglycerides can increase 50–100%. Depending upon the fat content of a meal, plasma triglyceride levels can remain high for up to 4 hours, even in healthy individuals [3].

Chylomicrons carry the triacylglycerol from the intestine into the lymphatic system and then into the circulatory system via the thoracic duct. As a consequence, the lungs and heart receive the initial flow of triacylglycerol-laden chylomicrons from the intestine after a meal. Indeed, the heart prefers fatty acid over glucose as a fuel source. In addition, chylomicrons contain apoB-48 (240,000 kD), apoA-IV (44,000 kD), apoC-II (8,837 kD), apoC-III (8,751 kD), and apoE (34,145 kD). ApoC-II activates lipoprotein lipase in the capillary endothelium of adipose tissue, heart, skeletal muscle, and lactating mammary glands. The lipase hydrolyzes the triacylglycerol to release free fatty acid to the target tissue, where the cell can utilize it as energy source or a fuel storage. The remnant chylomicrons, rich in cholesterol, return to the liver. In the liver, which synthesizes de novo both triacylglycerol and cholesterol, any excess triacylglycerol and cholesterol gets repackaged and re-exported to the circulation as VLDL [4].

12.3. LDL AND CHOLESTEROL TRANSPORT

In contrast, LDL does not play any significant role in transporting triacylglycerol after a meal. It has a major function in transporting cholesterol and regulating its metabolism. Moreover, releasing cholesterol from LDL does not require the action of any lipase or protease. The apoB-100 (513 kD) associated with LDL binds to the target cell surface receptor. Both the receptor and the LDL get endocytosed. Inside the cell, the LDL receptor fuses with lysosomes, where enzymes catalyze the release of the unesterified cholesterol for membrane biosynthesis. Alternatively, ACAT (acyl-CoA-cholesterol acyl transferase) can re-esterify cholesterol for storage [5]. The receptor then recycles to the cell surface.