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Review

Intestinal absorption of long-chain fatty acids: Evidence and uncertainties

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ABSTRACT

Over the two last decades, cloning of proteins responsible for trafficking and metabolic fate of long-chain fatty acids (LCFA) in gut has provided new insights on cellular and molecular mechanisms involved in fat absorption. To this systematic cloning period, functional genomics has succeeded in providing a new set of surprises. Disruption of several genes, thought to play a crucial role in LCFA absorption, did not lead to clear phenotypes. This observation raises the question of the real physiological role of lipid-binding proteins and lipid-metabolizing enzymes expressed in enterocytes. The goal of this review is to analyze present knowledge concerning the main steps of intestinal fat absorption from LCFA uptake to lipoprotein release and to assess their impact on health.

Contents

Abbreviations: ACBP, acyl-CoA-binding protein; ACS, acyl-CoA synthetase; BBM, brush border membrane; CM, chylomicron; DGAT, acyl-CoA diacylglycerol acyltransferase; ER, endoplasmic reticulum; FABPpm, plasma membrane fatty acid-binding protein; FACoA, long-chain-acyl-CoA esters; FAT/CD36, fatty acid transporter; FATP, fatty acid transport protein; FFA, free (non-esterified) fatty acids; I-FABP, intestinal fatty acid-binding protein; LBP, lipid-binding proteins; LCFA, long-chain fatty acids; L-FABP, liver fatty acid-binding protein; LPL, lipoprotein lipase; mAspAT, mitochondrial aspartate amino-transferase; MTP, microsomal triacylglycerol (triglyceride) transfer protein; PCTV, pre-chylomicron transfer vesicles; TAG, triacylglycerols.

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1. Introduction

Lipids account for about 40% of the calories ingested in Western countries, whereas nutritional recommendations are 5–10% lower. This excessive lipid intake, associated with a qualitative imbalance (excess of saturated fatty acids and cholesterol, too high $n-6/n-3$ ratio) strongly favours the development of obesity and associated diseases (atherosclerosis, non insulin-dependent diabetes, hypertension, cancer). From organs involved in lipid homeostasis, small intestine remains the most poorly known likely because it has been only considered for a long time as a selective barrier between outside and inside body environment.

In human diet, around 95% of dietary lipids are triacylglycerols (TAG), mainly composed of long-chain fatty acids (LCFA, number of carbons ≥ 16), the remaining being phospholipids (4.5%) and sterols. Because TAG cannot cross cellular membranes, they must be hydrolyzed before their subsequent metabolic use. Acid-stable gastric lipase partially digests TAG to form diacylglycerols and free fatty acids (FFA) in the stomach. This low lipase activity is essential for an efficient lipid emulsification [1]. Digestion of TAG continues in the small intestine mainly through the action of a colipase-dependent pancreatic lipase and leads to the release of 2-monoacylglycerols and LCFA (for a review, see [2]). In contrast to other energetic nutrients, LCFA are poorly soluble in aqueous solution. Moreover, they exhibit detergent properties potentially harmful for cellular integrity. To overcome these limitations, LCFA are successively dispersed into mixed micelles in intestinal lumen, bound to soluble lipid-binding proteins (LBP) in intestinal absorptive cells and, after re-esterification, are secreted into lymph as TAG-rich lipoproteins (Fig. 1A). During the post-prandial period, the small intestine produces and secretes chylomicrons (CM), whereas very low density lipoproteins (VLDL) are mainly synthesized during the interprandial periods. Once in the blood, TAG-rich lipoproteins are progressively hydrolyzed by the endothelial lipoprotein lipase (LPL) providing LCFA to peripheral tissues (muscles and adipose tissue). The TAG remaining in resulting small lipoproteins (remnants) are further hydrolyzed by the hepatic lipase; then remnants are cleared from blood by liver mainly *via* the LDL receptor-related peptide (Fig. 1A).

LCFA exert basic functions in the cell as membrane components, metabolic fuel, precursors of lipid mediators, regulators of ion-channels and modulators of gene expression [3]. They are also involved in various post-translational modifications of proteins (e.g. palmitoylation) affecting their cellular functions [4]. Therefore, digestion and absorption of dietary fat must be highly efficient to ensure a correct LCFA supply to the body. Nevertheless, LCFA being hydrophobic nutrients, their intestinal absorption remains complex. For didactic reason, it is classically depicted in three successive steps: cellular uptake, intracellular trafficking and lipoprotein synthesis/release (Fig. 1B).

2. Cellular LCFA uptake: diffusion and/or protein-mediated transfer?

LCFA transfer through the plasma membrane is a highly controversial question at the origin of several reviews [5–11]. By reason of their physicochemical properties, it was thought for a long time that LCFA uptake by cells only took place by diffusion. However,

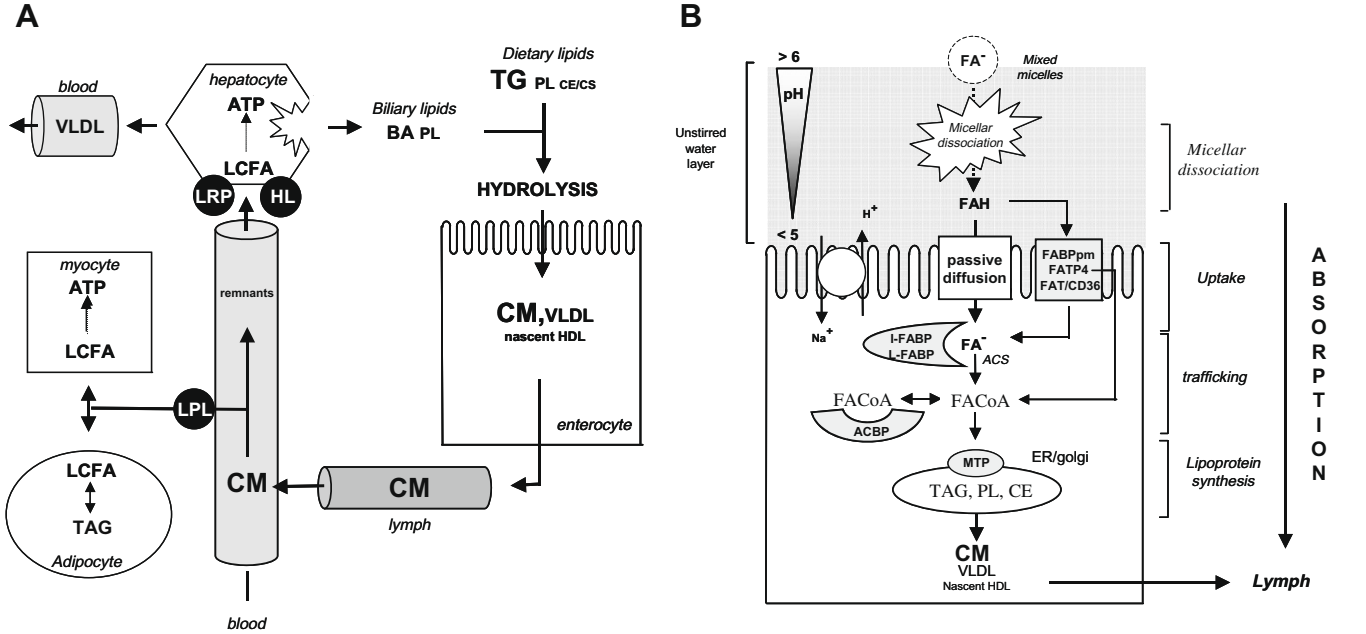

Fig. 1. The metabolic fate of dietary lipid in the body. (A) Circulation and metabolic fate of dietary lipid in the body. (B) The main steps and players involved in intestinal LCFA absorption are depicted: (1) micellar dissociation due to LCFA protonation mediated by the acidic microclimate lining the brush border membrane of enterocytes, (2) LCFA cellular uptake, (3) intracellular trafficking involving soluble lipid-binding proteins and (4) triacylglycerol-rich lipoprotein synthesis and exocytosis into the lymph. ACBP, acyl-CoA-binding protein; ACS, acyl-CoA synthetases; CS, cholesterol; ER, endoplasmic reticulum; FA^-, ionized long-chain fatty acids; FABPpm, plasma membrane fatty acid-binding protein; FAH, protonated long-chain fatty acids; FATP4, fatty acid transport protein 4; HDL, high density lipoprotein; I-FABP, intestinal fatty acid-binding protein; L-FABP, liver fatty acid-binding protein; HL, hepatic lipase; LPL, lipoprotein lipase; LRP, LDL-related peptide; MTP, microsomal triacylglycerol transfer protein; TAG, triacylglycerol (triglycerides); PL, phospholipids; CE, cholesterol esters; VLDL, very low density lipoproteins.