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Review

Lipoprotein-mediated lipid transport in insects: Analogy to the mammalian lipid carrier system and novel concepts for the functioning of LDL receptor family members

Kees W. Rodenburg*, Dick J. Van der Horst

Department of Biochemical Physiology, Faculty of Biology and Institute of Biomembranes, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands

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Abstract

In all animals, lipoproteins are used to transport lipids through the aqueous circulation. Lipids are delivered to mammalian cells by two different mechanisms: via endocytic uptake of the complete lipoprotein particle mediated by members of the low density lipoprotein (LDL) receptor (LDLR) family, or by selective delivery of lipoprotein-carried lipids at the cell surface, such as lipid uptake following the action of a lipoprotein lipase. Although many structural elements of the lipid transport system of insects are similar to those of mammals, insect lipoprotein-mediated lipid transport was thought to apply only to the latter concept, since the single lipoprotein acts as a reusable lipid shuttle. However, the recent identification of lipoprotein receptors of the LDLR family in insects suggests that lipid transport in these animals may also adopt the first concept. Yet, the endocytic properties of the insect LDLR homologue appear to deviate from those of the mammalian LDLR family members, resulting in the recycling of endocytosed lipoprotein in a transferrin-like manner. This indicates that a hitherto unknown as well as unexpected function can be added to the plethora of functions of LDLR family members. Analysis of the molecular mechanism of the ligand-recycling function of the insect receptor provides also new insight into the possible functioning of the mammalian family members. In the last several years, mammalian and insect lipoprotein-mediated lipid transport systems have been reviewed separately with respect to functioning and lipid delivery. This review, in which new and important developments in the insect field with respect to our understanding of lipid delivery are discussed with a particular focus on the involvement of the LDLR homologue, aims at comparing the two systems, also from an evolutionary biological perspective, and proposes that the two systems are more similar than assumed previously.

Keywords: Lipophorin; Ligand recycling; Receptor-mediated endocytosis; Selective lipid delivery; Non-selective lipid delivery; LpR; Transferrin

Abbreviations: apoE, apolipoprotein E; apoLp-II/I, apolipophorin II/I; apoLp-I, apolipophorin I; apoLp-II, apolipophorin II; apoLp-III, apolipophorin III; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; CHO, Chinese hamster ovary; DAG, diacylglycerol; EGFD, epidermal growth factor precursor domain; ERC, endocytic recycling compartment; FFA, free fatty acid; FH, familial hypercholesterolemia; HDL, high-density lipoprotein; HDLp, high-density lipophorin; ICD, intracellular domain; IDL, intermediate density lipoprotein; LBD, ligand binding domain; LDL, low-density lipoprotein; LDLp, low-density lipophorin; LDLR, LDL receptor; LLT, large lipid transfer; Lp, lipophorin; LPL, lipoprotein lipase; LpR, lipophorin receptor; LRP, LDLR related protein; LRP2, LDLR related protein 2; LRP8, apolipoprotein E receptor-2 (apoER2); LTP, lipid transfer particle; OLGD, O-linked glycosylation domain; RAP, receptor associated protein; SR-BI, scavenger receptor type BI; TAG, triacylglycerol; Tf, transferrin; TfR, transferrin receptor; TMD, transmembrane domain; TRL, TAG-rich lipoprotein; VgR, vitellogenin receptor; VLDL, very low density lipoprotein; VLDLR, VLDL receptor

* Corresponding author. Tel.: +31 30 253 9331; fax: +31 30 253 2837.
E-mail address: k.w.rodenburg@bio.uu.nl (K.W. Rodenburg).

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1. Introduction

Lipoproteins constitute vital complexes that allow water-insoluble lipids and other lipophilic components to be transported in the aqueous plasma of the circulatory system of animals. Mammals rely on two different triacylglycerol (TAG)-rich lipoproteins: chylomicrons produced in the intestine, that transport dietary (exogenous) lipids including cholesterol, and very low density lipoproteins (VLDL) synthesized and secreted by the liver, that carry out transport of endogenous TAG and cholesterol. During the process of selective (non-endocytic) delivery of their lipid cargo, involving TAG hydrolysis by lipoprotein lipase (LPL), the two different lipoproteins are concomitantly converted into smaller lipoprotein remnants. Thus, chylomicrons are converted into chylomicron remnants and VLDL into intermediate density lipoproteins (IDL) and LDL. During these conversions, in which high density lipoprotein (HDL) serves both as a donor and an acceptor for exchangeable apolipoproteins and lipid, the remnant particles become enriched in cholesteryl ester (CE), and are directed to the liver (Fig. 1; [1–4]), where the particles are taken up by receptor-mediated endocytosis and subsequently degraded in lysosomes. Additionally, LDL is taken up in peripheral cells by the same endocytic process to supply these cells with cholesterol (Fig. 2; for reviews, see [5–11]). The latter process can be characterized as non-selective lipid delivery, since the complete complex of lipid and protein components is taken up by cells and, except for a fraction of the associated exchangeable apolipoproteins in the case of chylomicron remnants, catabolized. The endocytic receptors involved are members of the LDL receptor (LDLR) family. In this endocytic process, these receptors characteristically release their ligand due to acidification of the endosomal lumen, and are recycled back to the cell surface for another round of endocytic uptake (for reviews, see [6,7,12–14]).

In contrast to mammals, insects use only one lipoprotein, termed lipophorin (Lp), to execute both exogenous and endogenous lipid transport. Lp has a density similar to mammalian HDL (~1.12 g/ml) and is therefore also referred to as high-density lipophorin (HDLp). Lp transports dietary lipids from the gut to the storage depot, the fat body, while additionally, the lipoprotein distributes stored or biosynthesized lipids to peripheral tissues (Fig. 3). The organization of this alternative lipid distribution system may be best understood from the perspective that the insect gut does not synthesize lipoprotein, and that the fat body combines the functions of the mammalian liver and adipose tissue in that it stores and synthesizes lipids, and synthesizes Lp, glycogen and other metabolically important compounds, respectively (for reviews, see [15–24]).

In mammals, the selective delivery of lipids appears to occur at the cell membrane of endothelial cells that surround the adipocytes. LPL hydrolyzes VLDL- or chylomicron-associated TAG to glycerol and free fatty acid (FFA) and subsequently, the FFA is transported across the membrane into the cell and resynthesized to TAG that is stored in lipid droplets (for reviews see [25–28]). In the conversion process of VLDL to IDL and LDL, and chylomicron to chylomicron remnant, HDL donates CE to the remnant lipoproteins (see for reviews [1–4]). This process of vectorial redistribution of lipid between these lipoproteins

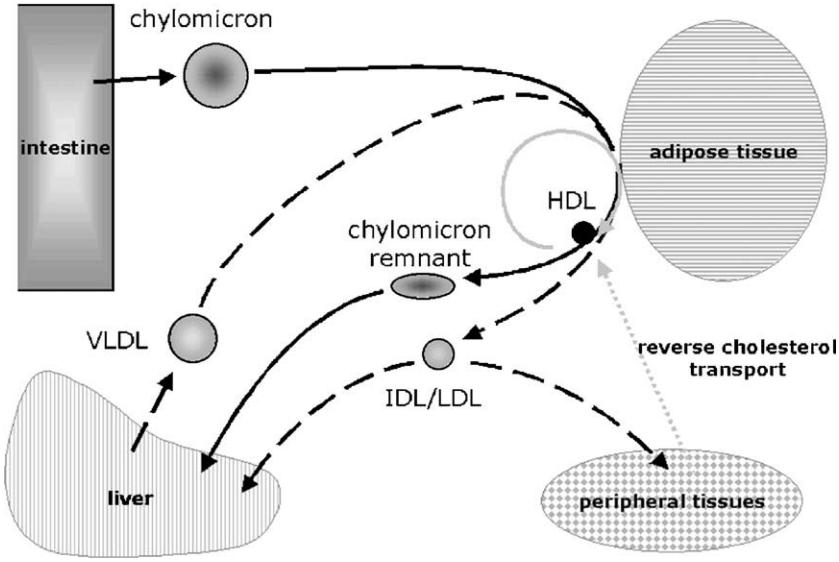

Fig. 1. Lipoprotein-mediated lipid transport in mammals involves several different lipoproteins. See the text for explanation. The different lipoproteins are represented by greyishly filled small circles and ellipse. The differently filled large forms represent organs. The different arrows indicate the different routes that are followed by the lipoproteins. A black arrow leaving tissue represents biosynthesis and secretion of lipoprotein, and an arrow entering tissue represents receptor-mediated endocytosis: solid black arrows, chylomicron transport route that upon delivery of TAG to adipocytes and HDL-derived CE exchange, yields a chylomicron remnant; solid grey arrow, HDL route, representing cholesterol scavenging and CETP-mediated CE conversion; dashed black arrows, VLDL route and the HDL-mediated conversion to IDL and LDL (IDL/LDL); dashed grey arrow, SR-BI-mediated reverse cholesterol transport route by which HDL scavenges cholesterol from cells.