faster lateral diffusion within the plane of a membrane, and more rapid intermixing than proteins. Proteins are destined for very specific locations (organelles) within the cell, whereas differences in the lipid composition between organelle membranes are not absolute. All organelle membranes contain more-or-less the same lipid classes, and only the ratio between these classes is unique and characteristic for a certain subcellular fraction. Finally, proteins contain signal sequences, which recognize the target membrane (e.g., via a specific receptor). No such signals exist in lipid molecules, which raises the question of the mechanism(s) of sorting of lipids within the cell. Investigations over the last 20 years have shown that lipid flux is a very complex process. It is very likely that different mechanisms of intracellular lipid transport exist in parallel, probably in most types of cells. Lipid transfer processes have been studied intensively with mammalian cells, but plant cells have also been used successfully for this purpose, and it is another area in which microorganisms have proved to be useful model cells. Most of our knowledge about lipid transfer processes and mechanisms comes from experiments in vitro. It is a matter of dispute which of these mechanisms are of relevance in vivo, and what contribution is made by each individual mechanism to membrane biogenesis and assembly. The present Multi-author Review gives an overview of lipid transport in various types of cells, the transport routes of the major classes of lipids, the mechanisms involved in intracellular lipid traffic, and the migration of lipids between cells and lipoproteins. The authors discuss these events and their contribution to the assembly of lipids into biological membranes.

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Interaction of lipid transfer protein with plasma lipoproteins and cell membranes

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Summary. The hydrophobic lipid components of lipoproteins, cholesteryl ester and triglyceride, are transferred between all lipoproteins by a specific plasma glycoprotein, termed lipid transfer protein (LTP). LTP facilitates lipid transfer by an exchange process in which cholesteryl ester and triglyceride compete for transfer. Thus, LTP promotes remodeling of the lipoprotein structure, and plays an important role in the intravascular metabolism of these particles and in the lipoprotein-dependent pathways of cholesterol clearance from cells. The properties of LTP, its mechanisms of action, its roles in lipoprotein metabolism, and its modes of regulation are reviewed along with recent data that suggest a possible role for this protein in directly modifying cellular lipid composition.
Key words. Lipid transfer protein; lipoprotein metabolism; lipoprotein remodeling; cholesteryl ester; triglyceride.

Plasma lipoproteins

Plasma lipoproteins can be classified into five categories: chylomicron, and very low density (VLDL), intermediate density (IDL), low density (LDL), and high density lipoproteins (HDL). Each class is heterogeneous in composition, reflecting, for the most part, the fact that each fraction contains a collection of particles that are at different stages of their metabolism. Thus, it is important to realize that lipoproteins are not the static structures that are isolated and characterized at a point in time, but rather, they are dynamic particles that reflect the sum of many different events which affect their composition. This review focuses on one of these events.

Generally, the structure of plasma lipoproteins can be divided into two domains – the coat and the core. The coat domain interacts with the aqueous environment and is composed mainly of phospholipid, unesterified choles-

terol and protein(s), whereas the core domain, which is surrounded by the coat, is predominantly cholesteryl ester and triglyceride[62]. Although the relative amounts of lipid and protein components, and the species of proteins present, vary widely among the major lipoprotein classes, they can be broadly segregated into triglyceride-rich lipoproteins (chylomicron and very low density lipoprotein) and cholesteryl ester-rich lipoproteins (low density and high density lipoproteins) based on their core lipid composition.

For the most part, lipids in the coat domain of lipoproteins are sufficiently soluble in the aqueous environment to permit their spontaneous exchange or transfer between lipoproteins[57]. In contrast, the core lipids, triglyceride and cholesteryl ester, do not readily transfer between isolated lipoproteins. For many years, based largely on studies in the rat, it was generally accepted that the non-transfer of cholesteryl ester and triglyceride also applied to the in vivo metabolism of these lipids. Thus, cholesteryl ester, but not triglyceride due to its hydrolysis by plasma lipases, was considered to be trapped within the core of a lipoprotein and could be used as a marker for the metabolic fate of that particle. However, studies by Nichols and Smith challenged this conclusion by demonstrating that during the long-term incubation of human plasma, one could observe a re-distribution of cholesteryl esters and triglycerides between lipoproteins[51]. Akanuma and Glomset also showed that radiolabeled cholesteryl esters synthesized in human plasma by lecithin : cholesterol acyltransferase were found in all lipoprotein classes although this enzyme uses HDL as its principal substrate[3].

Plasma lipid transfer activities

Zilversmit and colleagues were the first to report the isolation and partial characterization of a protein factor from rabbit plasma which could facilitate the transfer of cholesteryl esters between lipoproteins[80]. A specific cholesteryl ester transfer protein was subsequently partially purified from human lipoprotein-deficient plasma by this and other groups[35, 55]. The transfer of the other major core lipid, triglyceride, was also shown to be brought about by a similar molecular weight protein isolated from rabbit plasma[59]; however, these authors suggested that triglyceride and cholesteryl ester transfer proteins are distinct. Triglyceride transfer activity has also been observed in human plasma[7] and, similar to cholesteryl ester transfer activity, is essentially absent from rat plasma[7, 11].

By further characterization, Morton and Zilversmit subsequently demonstrated that triglyceride and cholesteryl ester transfer activities in human plasma co-purify through chromatographic steps leading to a 15,000-fold purification of both activities[48]. This protein, referred to herein as lipid transfer protein (LTP), was characterized as a glycoprotein with two molecular weight forms, 58,300 and 66,400, with a pI of 5.2. Similar proteins have been purified by Ihm et al.[34], Albers et al.[4], Tall et al.[71], and Abbey et al.[1]. Despite some differences in LTP preparations isolated by individual laboratories, the majority of published data support the suggestion that essentially all cholesteryl ester and triglyceride transfer activities are due to a single plasma protein – LTP.

Homogeneous LTP has recently been isolated by two laboratories[30, 37]. Pure LTP has a molecular weight of 74,000 as determined by SDS-polyacrylamide gel electrophoresis and is distinguished by its very high (45 %) percentage of nonpolar amino acid residues. Based on an analysis of a cDNA for LTP, LTP consists of 476 amino acids giving it a core molecular weight of only 53,108, with 4 asparagine glycosylation sites[18]. However, plasma LTP can be reduced to a protein of $\approx$ 60,000 by treatment with glycosidase F and neuraminidase, showing that N-linked sugars and sialic acid residues constitute the majority of the difference between the core and circulating protein[70]. The remaining difference between the core protein and deglycosylated LTP may reflect an incorrect assessment of the molecular weight of the intact protein since glycoproteins are known to behave aberrantly during SDS-electrophoresis[63]. LTP shows no structural homology with other plasma proteins or intracellular transfer proteins, and is remarkably more hydrophobic than all other plasma apolipoproteins[18]. mRNA for LTP is detectable in the liver, small intestine, adrenal and spleen; thus, like apolipoprotein E, the synthesis of LTP by peripheral tissues may reflect a role in cellular cholesterol metabolism or membrane biosynthesis[18].

Although transferred at considerably different rates, LTP demonstrates a broad specificity for the lipids that it can transfer[46, 48, 81]; all lipoprotein lipid components, except for unesterified cholesterol, are substrates for LTP. Even among a mixture of cholesteryl esters, human LTP preferentially transfers monounsaturated species over saturated and polyunsaturated cholesteryl esters[45]. The selective transfer of some lipids over others appears to be a property of LTP itself since LTP isolated from the rabbit shows a markedly different lipid selectivity than that observed for human LTP[81]. This species difference is somewhat remarkable given that the amino acid sequences of human and rabbit LTP are 81 % homologous and that two-thirds of those residues which differ are conservative changes[50].

Antibodies to LTP remove all detectable triglyceride and cholesteryl ester transfer activities from human plasma, confirming that the transfer of these lipids is promoted by a single protein[1,31]. However, removal of LTP from plasma decreases the facilitated transfer of phospholipid by only 30–60 %, indicating that plasma contains another phospholipid transfer factor. This protein, referred to as LTP-II[4] or as plasma phospholipid transfer protein[71], has no neutral lipid transfer activity; LTP-II will not be discussed further in this review.

Mechanism of LTP action

The mechanism by which LTP facilitates the transfer of lipids between plasma lipoproteins is only partly known. Two general mechanisms of transfer have been advanced. The carrier model of LTP activity proposes that LTP binds to an donor lipoprotein, picks up a lipid molecule or molecules, dissociates from the lipoprotein and then carries the lipid through the aqueous environment to an acceptor lipoprotein [10]. Alternatively, the collision-complex model proposes that LTP facilitates the formation of a ternary collision complex between donor lipoprotein, acceptor lipoprotein and itself, and it is within this complex that transfer occurs [36]. Existing data described below, while partially explaining the transfer mechanism, do not clearly support one mechanism over the other.

The physical interaction or binding of LTP with lipoproteins was first described by Pattnaik and Zilversmit [56]. LTP was shown to form isolatable complexes with HDL but not with LDL or VLDL under the non-equilibrium conditions used. However, the association of LTP with LDL and VLDL could be shown when the negative surface charge of these lipoproteins was increased by succinylation or by phospholipase A_2 treatment. Conversely, the interaction with HDL could be disrupted by lowering the pH to 4.5 or adding divalent cations to the assay. Collectively, these data suggest that lipoprotein phospholipids are the binding sites for LTP. The importance of these binding interactions for the lipid transfer process was shown by subsequent studies under steady state conditions [42]. The binding of LTP to all lipoproteins was demonstrated and was found to exhibit saturation with increasing LTP concentration, with an apparent K_m of $\approx$ 25 nM for VLDL, LDL, and HDL. The extend of lipid transfer activity was shown to parallel this binding event, substantiating an assumption inherent in both transfer models that the transfer mechanism involves the binding of LTP to the surface of lipoproteins. This conclusion is supported by the findings that agents which affect the molecular organization of the phospholipid coat of lipoproteins also perturb LTP activity [43, 49, 53].

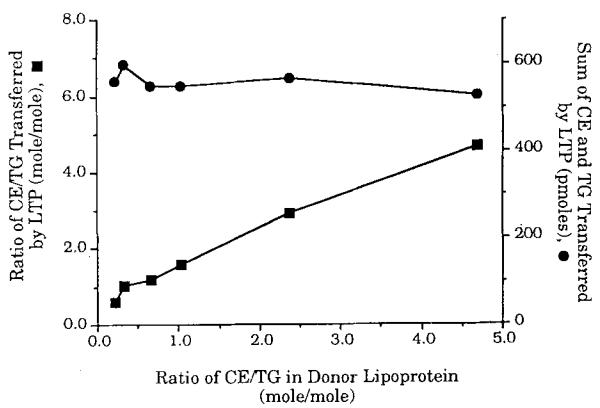

Figure 1. Effect of lipoprotein core lipid composition on LTP activity. Reconstituted HDL was synthesized to contain the indicated CE/TG lipid composition, and then used as the donors of radiolabeled CE and TG for transfer to LDL. Both the total amount of CE plus TG transferred and the ratio of CE to TG transferred by LTP are shown versus the lipid composition of the donor lipoprotein. Similar data have been previously published [46].
CE, cholesteryl esters; TG, triglycerides.

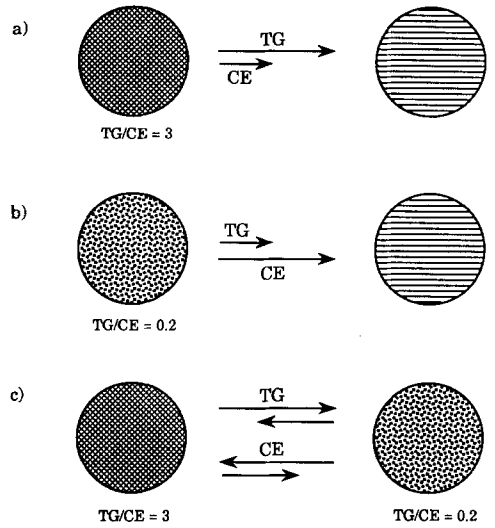

Figure 2. Effect of lipoprotein composition on lipid transfer. Panels *a* and *b* describe the LTP-mediated, unidirectional transfer of lipids from the donor lipoprotein shown to an acceptor. Panel *c* describes the initial, bidirectional transfer of lipids between the two lipoproteins shown. Relative transfer rates are indicated by the length of the arrows. TG/CE values are mole ratios [64].
CE, cholesteryl esters; TG, triglycerides.

The transfers of different lipid classes by LTP are not independent events. Using reconstituted lipoproteins with defined cholesteryl ester and triglyceride compositions, it was shown that the selection of cholesteryl ester or triglyceride for transfer by LTP is linearly dependent on the ratio of these two lipids in the reconstituted lipoprotein (fig. 1). The core lipid composition of the acceptor lipoprotein had no apparent effect on the selection of triglyceride or cholesteryl ester for transfer [46]. Additionally, over a range of cholesteryl ester to triglyceride ratios encompassing those found in plasma lipoproteins, the sum of cholesteryl ester and triglyceride transferred by LTP was essentially constant (fig. 1). Together these data show that cholesteryl ester and triglyceride compete for transfer with the extent of competition being defined by the chemical composition of the donor lipoprotein. The competition of these two lipids for transfer is consistent with the recent observation that these lipids compete for binding to a putative active site on LTP [69]. On the other hand, the transfer of phospholipid by LTP appears to be independent of cholesteryl ester and/or triglyceride transfers [46].

The competition of triglyceride and cholesteryl ester for transfer is illustrated in figure 2. Panels a and b describe the initial lipid transfer events for two lipoproteins containing different triglyceride to cholesteryl ester ratios.

For the triglyceride-rich lipoproteins, the transfer of triglyceride is greater than cholesteryl ester, but for the cholesteryl ester-rich lipoproteins, cholesteryl ester transfer exceeds triglyceride transfer. Furthermore, since the LTP-mediated transfer of lipids between two lipoproteins is a bidirectional process[10,12,36,46] rather than the unidirectional transfer processes described in figure 2a and b, the competition data described above and a variety of in vitro experiments indicate that LTP promotes two distinct lipid transfer processes: 1) an exchange reaction, which equilibrates the molecular species of a given lipid between lipoproteins, and 2) a net transfer reaction, which effects changes in the lipid composition of lipoproteins. At least for the transfer between two lipoproteins which initially have different triglyceride to cholesteryl ester compositions, these two processes occur simultaneously. Figure 2c describes these lipid transfer events between such lipoproteins, and is representative of the transfers that would occur between plasma HDL and VLDL. LTP promotes the bidirectional exchange of triglyceride for triglyceride, and the exchange of cholesteryl ester for cholesteryl ester (homoexchange). Additionally, since the lipoproteins differ in their triglyceride to cholesteryl ester ratios, LTP facilitates a greater transfer of triglyceride from the more triglyceride-rich lipoprotein to the more cholesteryl ester-rich lipoprotein, and conversely for cholesteryl ester transfer, resulting in a mass transfer of triglyceride from the first lipoprotein to the second and cholesteryl ester transfer from the second lipoprotein to the first (heteroexchange). For the most part, the mass transfer of cholesteryl ester and triglyceride between lipoproteins does not change the total neutral lipid content of lipoproteins[4,16,46,77], indicating that the heteroexchange process involves the equimolar exchange of triglyceride and cholesteryl ester.

An obvious extrapolation of the transfer processes described in figure 2c is that, given adequate time, LTP would facilitate an equilibration of the neutral lipid cores of two initially different lipoproteins, resulting in their having the same triglyceride to cholesteryl ester ratio. This prediction is borne out in vivo. In human plasma, LDL and HDL have rather long resident times and their triglyceride to cholesteryl ester ratios are nearly the same, however, VLDL has a much shorter resident time and its neutral lipid core is only partially equilibrated[11,64]. But in rats, which lack active LTP, the triglyceride to cholesteryl ester ratio in LDL and HDL are greatly different even though these lipoproteins have relatively long plasma resident times[9,41,54].

Role of LTP in lipoprotein metabolism

The ability of LTP to facilitate the dynamic remodeling of lipoprotein composition, both by homogenizing the molecular species of a given lipid class, which may be of endogenous or exogenous origin, and by mediating net changes in neutral lipid composition, suggests that it may play an important role in the intravascular metabolism and plasma clearance of lipoproteins. Current data suggest that LTP participates in the metabolism of VLDL and in the pathways involved in the clearance of cholesterol to the liver.

A) Catabolism of very low density lipoprotein

The putative role of LTP in the metabolism of very low density lipoprotein to low density lipoprotein is illustrated in figure 3. Although a major step involved in the conversion of VLDL to LDL is the hydrolysis and removal of $> 95\,\%$ of the triglyceride by the action of lipoprotein lipase, VLDL also contains more cholesteryl esters than will fit into an LDL particle[64]. LTP is proposed to facilitate the removal of this excess cholesteryl ester. As VLDL is hydrolyzed by lipoprotein lipase (step 1), a remnant particle is generated which contains all the original cholesteryl ester but decreasing amounts of the triglyceride, resulting in a particle which has a triglyceride to cholesteryl ester ratio that is less than that in LDL or HDL. Due to this ratio, the remnant particle becomes a better cholesteryl ester donor for transfer via LTP than LDL or HDL and, thus, LTP can facilitate the net removal of cholesteryl ester from the remnant to these lipoproteins in return for triglyceride (step 2). This triglyceride is, in turn, hydrolyzed by lipoprotein lipase (step 3). Through multiple cycles of LTP and lipase activities (steps 2 and 3), the remnant is converted to a particle that contains the cholesteryl ester to triglyceride ratio and the number of neutral lipid molecules present in a circulating LDL.

Several lines of evidence support this pathway. In vitro hydrolysis of VLDL with lipase forms a remnant particle which contains the full complement of cholesteryl ester, has a triglyceride to cholesteryl ester mole ratio of ≈ 0.1 which is much smaller than the ratio of ≈ 0.2 found in LDL or HDL, and has a molecular weight twice that of LDL[14]. Secondly, intermediate density lipoproteins (VLDL remnants) can be depleted of their cholesteryl esters and enriched with triglyceride by LTP, and this triglyceride can in turn be hydrolyzed by lipase to yield a smaller, more LDL-like lipoprotein in vitro[16]. Consistent with these observations, patients with LTP deficiency[79] and animals with low LTP activity[54] have low levels

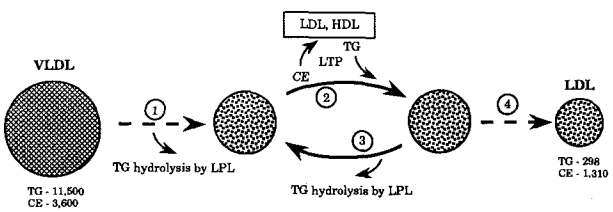

Figure 3. Role of LTP in VLDL metabolism. See text for description of steps 1–3, step 4 reflects multiple rounds of steps 2 and 3. Although presented stepwise, events are believed to occur concomitantly. Nonstandard abbreviations: LPL, lipoprotein lipase; CE, cholesteryl ester; TG, triglyceride. TG and CE numbers refer to the number of molecules of each in the lipoprotein shown[64].

of LDL, and animals with low plasma triglyceride levels accumulate large cholesteryl ester-rich 'LDL' particles which can be converted in vitro to nearly normal appearing LDL by incubation with LTP, lipase, and a lipoprotein source of triglyceride [15].

B) Role of LTP in HDL metabolism

HDL plays a central role in the homeostasis of cholesterol, facilitating the removal of cholesterol from cellular membranes and subsequently serving as the site of action where lecithin: cholesterol acyltransferase converts the cholesterol to cholesteryl ester, thus lowering plasma unesterified cholesterol concentrations. This process, termed reverse cholesterol transport, functions to deliver cellular cholesterol, in the form of lipoprotein cholesteryl ester, to the liver where it can be eliminated from the body [25]. A key regulatory point of reverse cholesterol transport is the consumption of cholesterol by lecithin: cholesterol acyltransferase since the activity of this enzyme is essential to maintaining a concentration gradient down which cellular cholesterol can flow. Lecithin: cholesterol acyltransferase, which accounts for almost all of the cholesteryl esters in circulating lipoproteins [25], is regulated by feedback inhibition of its product cholesteryl ester [9, 21]. As illustrated in figure 4, during the action of lectithin: cholesterol acyltransferase, HDL_3, a preferred substrate, is converted to the larger HDL_2 as cholesteryl esters accumulate within the HDL particle (step 1), resulting in a lipoprotein that is a poorer substrate for the enzyme [8]. LTP is proposed to play an important role in reverse cholesterol transport by facilitating the removal of cholesteryl ester from HDL which enhances lecithin: cholesterol acyltransferase activity. Cholesteryl ester removal proceeds in a manner analogous to that described for VLDL metabolism where LTP mediates the removal of cholesteryl ester to LDL or VLDL in return to triglyceride (step 2), and then the triglyceride is hydrolyzed by hepatic lipase to yield a smaller HDL which has less cholesteryl ester (step 3).

A role for LTP in reverse cholesterol transport is supported by the finding that LTP, lipase, and VLDL incubated in vitro with HDL_2 converts it toward an HDL_3-like particle that is smaller and contains $^1/_3$ of its original cholesteryl ester [13]. Additionally, HDL, which has been intentionally depleted of cholesteryl ester and enriched with tryglyceride by LTP, stimulates lecithin: cholesterol acyltransferase activity more than native HDL [32, 33]. And finally, the synthesis of cholesteryl esters in plasma by lecithin: cholesterol acyltransferase is only slightly stimulated by the addition of more of the enzyme to plasma, but is markedly increased by the addition of both lecithin: cholesterol acyltransferase and LTP [4].

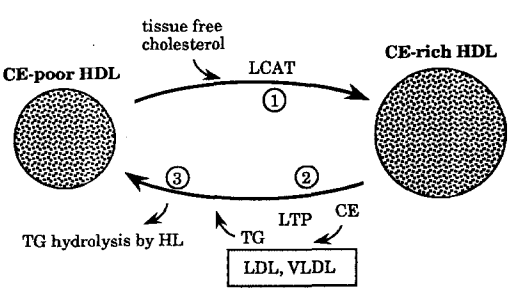

Figure 4. Role of LTP in HDL metabolism. See text for description of steps. Non-standard abbreviations: HL, hepatic lipase; LCAT, lecithin: cholesterol acyltransferase; CE, cholesteryl ester; TG, triglyceride.

The role of LTP in the metabolism of HDL is further illustrated by in vivo experiments. In rats, which normally have low detectable LTP activity, the infusion of LTP results in the loss of cholesteryl ester-rich HDL particles [27, 28]. Conversely, in rabbits infused with antibody to LTP [2, 78], or in humans deficient in LTP [38], cholesteryl ester-enriched, large HDL particles accumulate. Moreover, in these experiments the overall rate of cholesterol clearance from plasma was positively correlated with the presence of LTP activity, showing that the transfer of cholesteryl esters to LDL and VLDL markedly increases the hepatic removal of cholesterol from the circulation. This finding is consistent with the observation that, in humans, HDL turnover is adequate to account for only ~20% of the plasma clearance of cholesterol, with the bulk of lecithin: cholesterol acyltransferase-generated cholesteryl esters being cleared by the hepatic uptake of LDL [9]. This illustrates the importance of LTP in transferring cholesteryl esters from their site of synthesis in HDL to other lipoproteins.

Regulation of LTP activity

Considering the important role of LTP in lipoprotein metabolism, it is not unlikely that its activity may be subject to multiple regulatory steps. Three possible modes of regulation are described below.

A) Regulation by lipoprotein composition

Unlike cellular membranes, the lipid composition of lipoproteins varies greatly in response to diet and other stimuli. Numerous studies have shown that the chemical composition of lipoproteins affects their ability to function as LTP substrates. For example, modification of lipoprotein surface properties by prostaglandin E_1 [49] or by certain apoproteins [53] has been shown to markedly increase LTP-mediated neutral lipid transfer. Additionally, lipoproteins from subjects with hyperbetalipoproteinemia or dysbetalipoproteinemia [24], or from patients with end-stage renal disease undergoing hemodialysis [17], support reduced rates of cholesteryl ester transfer compared to lipoproteins from normolipemic individuals. In contrast, lipoproteins from insulin-dependent diabetics [6], from hypertriglyceridemic rabbits [40], those collected from plasma during alimentary lipemia [73], or lipoproteins isolated after exposure to lipoprotein lipase [61, 72] facilitate increased cholesteryl ester transfer activity when compared to control lipoproteins assayed under standardized conditions. The molecular

mechanisms responsible for these altered reactivities with LTP are unknown, but likely relate to the compositional changes that occur in these lipoproteins. While some of these compositional changes may influence the binding of LTP to the lipoprotein surface, others may perturb or enhance its activity once bound. An example of this latter possibility is described below.

Alteration in the free (unesterified) cholesterol content of lipoproteins, expressed as the free cholesterol to phospholipid ratio, is a common feature of lipoproteins isolated from various hyperlipemic individuals and from diabetics[22,23], and an elevated free cholesterol to phospholipid ratio in plasma is a strong risk factor for ischemic heart disease[39]. We have recently reported that the level of free cholesterol in lipoproteins is a potent modifier of LTP activity and function[43]. Free cholesterol was shown to separately alter the transfer of both triglyceride and cholesteryl ester by LTP, and the effect of free cholesterol on lipid transfer was unique for each lipoprotein class. Generally, the effects of free cholesterol on triglyceride and cholesteryl ester transfers were consistent with the effects that cholesterol has on the solubility of these lipids in phospholipid. This suggests that free cholesterol may perturb LTP activity by altering the concentration of triglyceride and cholesteryl ester available at the surface of the lipoprotein. Overall, elevations in free cholesterol levels stimulated the ability of LTP to mediate the net mass transfer (heteroexchange) of cholesteryl ester from HDL to other lipoproteins. This result suggests that free cholesterol is a positive modulator of the pathways involved in its clearance from the body – reverse cholesterol transport.

B) Regulation of LTP by other plasma proteins

Although LTP activity does not require any particular apolipoprotein and is not affected by inhibiting the activity of lecithin:cholesterol acyltransferase in plasma[34,51], it is regulated by other plasma proteins. Regulation of LTP was first suggested by studies showing that homozygous type II hypercholesterolemics have 3–4-fold more LTP activity in their lipoprotein-deficient plasma than controls, but only $^1/_3$ the activity of controls in a partially purified LTP preparation[55]. To date there are several candidate proteins which may regulate LTP activity. Apolipoprotein A–I, the major protein component of HDL, may inhibit LTP activity[66], although this has not been confirmed by other investigators[52]. Conversely, the phospholipid transfer protein from plasma (LTP II) has been shown to stimulate the activity of LTP in vitro, however it remains to be determined if this stimulatory activity has in vivo relevance[76]. The best described regulator of LTP to date is a 29,000–35,000 molecular weight acidic glycoprotein termed simply LTP inhibitor protein or LTPI[47,52,66]. LTPI suppresses the transfer of both triglyceride and cholesteryl ester from a given donor lipoprotein by a similar extent[47]. However, lipid transfers from different lipoprotein classes are not equally suppressed, suggesting that LTPI may actually focus the activity of LTP by preferentially suppressing some transfer events over others rather than simply suppressing LTP activity in general. LTPI suppresses LTP activity by disrupting the binding of LTP to its substrate lipoproteins[42]; this disruption likely occurs by the competition of LTP and LTPI for a common binding site on lipoproteins, which explains why the extent of inhibition is directly dependent on lipoprotein concentration[42,66]. When LTPI is removed from lipoprotein-deficient human plasma, LTP activity is increased by up to 50 %[75]. The best evidence that LTPI has a physiological role in regulating LTP comes from studies from the rat. In vivo the rat has no measurable LTP activity[54], yet, when LTPI is removed in vitro, LTP activity is present at a level about $^1/_3$–$^1/_2$ that in humans[75]. A paradox, however, is why does the rat have LTP, yet totally inhibit its activity in vivo? Perhaps LTP has other, as yet unknown, functions which are not inhibited by LTPI.

C) Regulation of LTP biosynthesis

The wide distribution of LTP mRNA among various tissues suggests that LTP is synthesized by a variety of cell types. Indeed, in culture, hepatocytes (HepG2), monocyte-derived macrophages, and intestinal enterocyte epithelium (CaCo-2) secrete LTP into the media[19,20,74]. Although little is known about the factors which regulate the secretion of LTP by these cells, secretion appears to be coupled to lipid metabolism. CaCo-2 cells increase LTP secretion in response to fatty acids in the media[20], and the secretion of LTP by monocyte-derived macrophages is enhanced by conditions which lead to cholesteryl ester loading of these cells[5]. These observations are consistent with in vivo studies in rabbits where plasma levels of LTP were increased by hypercholesterolemia (exogenously or endogenously induced) and the rise in LTP correlated temporally with the increase in plasma cholesterol levels[65], leading the authors to suggest that the synthesis of LTP may be linked to hepatic cholesterol secretion[58]. This linkage is consistent with the proposed role of LTP in facilitating events which augment cholesterol delivery to the liver for excretion.

LTP-cells interactions

In addition to the well-established role of LTP in mediating lipoprotein-lipoprotein lipid transfers, several studies have suggested that LTP may also facilitate lipid transfers with cells. The ability of LTP to transfer lipids between lipoproteins, between lipoproteins and phospholipid-cholesterol liposomes[48], between lipoproteins and Intralipid[77], and between isolated smooth and rough endoplasmic reticulum[29], clearly shows that LTP can utilize a wide variety of phospholipid-containing membrane surfaces as substrate. Thus, LTP-mediated transfer from or to cells seems not only plausible but likely.

LTP has been shown to promote the 'transfer' of

cholesteryl ester associated with the extracellular matrix of smooth muscle cells to the culture medium [68]. Transfer was both time and LTP concentration dependent and was stimulated by the presence of triglyceride-rich lipoproteins in the media. LTP also facilitated the transfer of cholesteryl ester from smooth muscle cells themselves to the medium if these cells were first fixed and permeabilized; similar results were observed for cultured macrophages under the same assay conditions [67]. Collectively, these results suggest that LTP may promote cholesteryl ester efflux from disintegrating cells or connective tissue elements, and thereby play a role in cholesteryl ester homeostasis in tissue.

Two recent studies indicate that LTP may also participate in the cholesteryl ester metabolism of intact, living cells. LTP promoted the uptake of cholesteryl esters from HDL into hepatocytes, smooth muscle cells, and fibroblasts in culture by a pathway that was independent of the metabolism of the whole HDL particle [26]. Although a recent study offers an alternative explanation for these results with hepatocytes which is independent of a direct transfer of cholesteryl ester to these cells [60], this explanation does not apply to the other cell types studied. Unlike that observed with hepatocytes and smooth muscle cells, LTP promoted the *net removal* of cholesteryl esters from cultured macrophages which had been loaded with this lipid by preincubation with acetylated low density lipoprotein [44]. This transfer was stimulated by the presence of LDL or HDL in the media, and the transferred cholesteryl esters became associated with these lipoproteins. However, LTP could not facilitate cholesteryl ester uptake by the cells from lipoproteins, indicating that LTP activity with these cells promoted only lipid efflux (unidirectional transfer), which distinguished these transfers from those between lipoproteins. Collectively, these data strongly support a role for LTP in modulating cellular sterol levels, which could directly impact on cellular membrane integrity. The synthesis of LTP by some of these cell types in vivo could provide high local concentrations of transfer protein which would greatly facilitate a role of LTP in cellular sterol metabolism.

Summary

Plasma lipoproteins are dynamic particles which undergo continual remodeling of their lipid components during their lifetime in the circulation. In humans, LTP plays a key role in this remodeling by facilitating the homogenization of cholesteryl ester and triglyceride molecular species, and by promoting the equimolar exchange of cholesteryl ester for triglyceride. LTP is likely to be a key component in the catabolic pathway of VLDL to LDL and in the recycling of extrahepatic cholesterol to the liver for excretion. The potential importance of LTP seems to be underscored by the existence of regulatory plasma proteins, and by the modulatory effects of lipoprotein composition which, at least in vitro, selectively alter LTP activity toward lipoprotein substrates. Furthermore, LTP may play an important role in regulating the lipid composition of cells either by directly interacting with cellular membranes, or by altering the composition and concentrations of lipoproteins which are taken up via specific cellular receptors.

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The assembly of lipids into lipoproteins during secretion

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Summary. The process of assembly and secretion of lipoproteins is discussed with particular reference to the role of lipids. The majority of circulating lipoproteins is produced by the liver (80 %) with the remainder being supplied by the intestine. The liver secretes both very low density lipoproteins and high density lipoproteins, but the assembly and secretion of these two types of particles may follow different routes. The major lipid components of lipoproteins are triacylglycerols, cholesterol, cholesterol esters and phospholipids. The biosynthesis of these lipids occurs on membranes of the endoplasmic reticulum, with many of the enzymes also being present in the Golgi; the roles of these two subcellular organelles in the assembly of lipoproteins are discussed. There appears to be a compartmentalization of lipids in cells, such that defined pools, often those newly-synthesized, are preferred, or even required, for lipoprotein assembly. The process of hepatic very low density lipoprotein secretion appears to be regulated by the supply of lipids. Indeed, the synthesis of new lipid may be a major driving force in lipoprotein assembly and secretion.
Key words. Lipoprotein secretion; very low density lipoproteins; high density lipoproteins; lipid compartmentalization.

Introduction

Great interest in lipid and lipoprotein metabolism has been generated recently because the risk of atherogenesis is now recognised as being related to the blood levels of lipoproteins. The four major classes of circulating lipoproteins are: chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL), which are classified according to their densities. The basic structure of the approximately spherical lipoprotein particles consists of a hydrophobic core (mainly triacylglycerols and cholesterol esters) surrounded by a hydrophilic coat comprising a monolayer of amphipathic lipids (cholesterol and phosholipids) interspersed with a mixture of specific proteins called apo(lipo)proteins. The hydrophilic coating of lipoproteins permits the hydrophobic core lipids to be transported in the aqueous environment of blood to other tissues.

Lipoproteins are secreted by liver and intestine, with the majority of the apoproteins ($\approx$ 80 %) derived from the liver[83]. The intestine produces the large triacylglycerol-rich chylomicrons and VLDL, and some HDL, whereas the liver secretes VLDL and HDL. There are two related