minireview

Plasma lipid transfer proteins

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Introduction

The composition of the plasma lipoproteins is continuously modified during their intravascular metabolism, as a result of a dynamic exchange and net transfer of lipids between particles or between particles and cells. Specialized proteins, the plasma lipid transfer proteins, facilitate the transfer and exchange of phospholipids, cholesteryl esters, and triglycerides between the lipoproteins. Although there is little published evidence, plasma lipid transfer proteins can probably also influence the transfer of lipids between lipoproteins and cells.

Purification of lipid transfer proteins

The incubation of human plasma results in a net transfer of triglycerides from very low density lipoproteins (VLDL) to low density lipoproteins (LDL) and high density lipoproteins (HDL), with a reciprocal transfer of cholesteryl esters from HDL and LDL to VLDL (1). A protein that facilitates the transfer and exchange of cholesteryl esters and triglycerides between the lipoproteins has been purified from human plasma (2, 3). Although the lipid transfer activities were initially assigned to apoD (2), subsequent studies found that antisera to apoD did not remove cholesteryl ester transfer activity from plasma fractions (4). More recent purifications have shown that cholesteryl ester transfer and exchange are mediated by a protein or proteins with an apparent molecular weight of approximately 60,000 to 70,000 as judged by SDS gel electrophoresis, or by gel filtration chromatography (5–8). However, no laboratory has reported sufficient characterization of the purified material to be sure that it is truly homogeneous; well characterized, monospecific antisera have not yet been described.

Although the cholesteryl ester transfer protein (CETP) also facilitates exchange of phospholipids, there is evidence that plasma contains a separate phospholipid transfer protein (PTP) which does not mediate transfer of cholesteryl esters (8). The PTP, which enhances transfer of phospholipids from unilamellar phospholipid vesicles into HDL, was purified from the plasma d > 1.21 g/ml fraction and separated from the CETP during ion exchange chromatography (8, 9). The most purified preparation showed a major component of apparent M_r 41,000 (8). The PTP is able to mediate transfer of a wide variety of phospholipids including phosphatidylcholines, sphingomyelin, phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, phosphatidic acid, galactosylcerebroside, and diacylglycerol (10). Although the CETP and PTP are referred to as *transfer* proteins, both proteins may mediate either transfer or exchange of lipids depending on the composition of the donor and acceptor lipoproteins (11–13).

Mechanism of action and inhibitors

Morton and Zilversmit (12) showed that highly purified CETP promotes both the exchange and net transfer of triglyceride and cholesteryl ester, and that the net transfer process proceeds by a reciprocal exchange of triglyceride and cholesteryl ester without net transfer of core lipids between lipoproteins, i.e., net transfer is mediated by a hetero-exchange process.

Kinetic studies suggest that the CETP enhances the exchange of lipids during formation of a ternary collision complex involving donor and acceptor lipoprotein and CETP (14). This model predicts that formation of the collision complex is energetically favored if CETP is bound to donor or acceptor lipoprotein prior to formation of the collision complex (14). Subsequent studies have shown that CETP-mediated transfer is favored by alterations in lipoprotein composition which result in increased binding of CETP to the lipoprotein (15), consistent with the model. Alternatively, CETP may act as a carrier of lipid between donor and acceptor lipoproteins, i.e., a ping-pong mechanism (16). However, there is some kinetic evidence to refute this hypothesis (14). Also, a shuttle mechanism does not readily explain the enhancement of lipid exchange that occurs with increased binding of CETP to either donor or acceptor lipoprotein (15).

The lipoprotein-free fraction of plasma from several species, including those with and without significant

Abbreviations: VLDL, very low density lipoproteins; LDL, low density lipoproteins; HDL, high density lipoproteins; CETP, cholesteryl ester transfer protein; PTP, phospholipid transfer protein.

cholesteryl ester transfer activity, may contain inhibitors of CETP. An inhibitor of cholesteryl ester and triglyceride transfer with an apparent M_r of 32,000 has been purified from human plasma (17). ApoA-I (17), apoE (18), and fatty acid-free albumin (15) may also inhibit CETP-mediated cholesteryl ester transfer. Fatty acid-free albumin inhibits transfer by decreasing the binding of CETP to the lipoprotein surface (15); a recent study indicates that the inhibitor of M_r 32,000 also decreases lipoprotein binding of CETP (19). These proteins probably compete for or modify CETP binding sites in the lipoprotein surface. It is presently unknown whether inhibitors are active in vivo or can account for differences in facilitated lipid transfer in various species or in different metabolic states.

The plasma PTP is able to mediate the net transfer of phospholipids from vesicles into HDL, resulting in the formation of larger, less dense HDL particles (8, 9, 13). The PTP can also enhance net transfer and exchange of phospholipids between VLDL and HDL (11). Whether net transfer or exchange of phospholipids predominates may depend on the chemical potential of phospholipid in the lipoprotein surface, e.g., net transfer into lipoproteins may occur from small vesicles or from a surface rich in phospholipids as a result of triglyceride hydrolysis. The *spontaneous* exchange of phospholipids between lipoproteins probably takes place by diffusion of monomeric phospholipid molecules through the aqueous phase; the desorption of phospholipid from the donor lipoprotein into the aqueous phase represents the major rate-limiting step and the free energy barrier is proportional to the hydrophobicity of the phospholipid fatty acid chain (20–23). The mechanism of the *facilitated* exchange mediated by PTP appears to be different from that of spontaneous exchange (10). Whereas the rate of the spontaneous exchange of a series of different phospholipids was inversely proportional to their hydrophobicity, the PTP-mediated exchange was independent of hydrophobicity (10). This suggests that the PTP does not promote desorption of phospholipid monomers into the aqueous phase (10). Rather, the PTP may enhance exchange during formation of a collision complex of donor and acceptor lipoproteins, analagous to the suggested mechanism of action of CETP (5), or the PTP may act as a carrier of phospholipid between lipoproteins, analogous to the intracellular phosphatidylcholine-specific exchange protein (24).

Binding to lipoproteins and distribution in plasma

Binding of CETP to the lipoprotein surface appears to involve the phosphocholine moieties of phosphatidylcholine and also negatively charged lipoprotein-associated fatty acids (25). CETP can be completed dissociated from its lipoprotein binding sites by lowering the pH of plasma to 5.5 (26). Since fatty acids in lipoproteins or micelles probably have elevated apparent pKas, this finding is consistent with an essential role of negatively charged lipoprotein fatty acid (15). Alternatively, a titratable amino acid residue could be involved in the binding of CETP to the plasma lipoproteins.

Both the PTP and CETP are associated predominantly with the HDL in fasting plasma. During density gradient ultracentrifugation, PTP and CETP are recovered in the smaller, denser HDL (largely between density 1.18–1.25 g/ml); with prolonged ultracentrifugation they dissociate into the lipoprotein-free fraction (9, 25). On agarose chromatography, CETP elutes with the smaller HDL (25, 26) which are known to be enriched in apoA-I and LCAT (17, 25, 27). In human plasma, a small, variable fraction of CETP is not lipoprotein-bound as assessed by agarose or apoA-I affinity chromatography (26). Although CETP shows little binding to VLDL and LDL as assessed by co-incubation followed by gel filtration (25, 26), CETP seems to form unstable complexes with VLDL and LDL immobilized on agarose (19). It remains to be seen whether similar unstable complexes are present in plasma and whether they are related to the cholesteryl ester transfer process.

Role of lipid transfer proteins in lipoprotein metabolism

During lipolysis of chylomicrons and VLDL, there is transfer of phospholipids from the triglyceride-rich lipoproteins into HDL (28–30). The PTP probably mediates the transfer of phospholipids. The rates of spontaneous exchange of lipoprotein phospholipids are too slow to account for those occurring during lipoprotein metabolism (9, 23). The spontaneous transfer of phospholipid from vesicles into HDL proceeds slowly and continuously during a 24-hr incubation (31). By contrast, when vesicles are injected into rats or incubated in plasma or with plasma fractions containing the PTP, the transfer into HDL is completed with a $t_{1/2}$ of less than 30 min (9, 31, 32). In vivo the $t_{1/2}$ for transfer of chylomicron phospholipids into HDL is about 15 to 30 min, suggesting that the phospholipid transfer is a facilitated process (30). The net transfer of phospholipids into HDL is followed by movement of cholesterol into HDL from other lipoproteins and cells, thereby providing both substrates required by LCAT (phospholipids and cholesterol) (30). Also, since LCAT probably prefers to use unsaturated fatty acids derived from the *sn*-2 position of phosphatidylcholine, the PTP-mediated exchange of phospholipids between HDL and other lipoprotein may serve to replenish unsaturated fatty acid-containing phospholipids in HDL (11).

CETP redistributes LCAT-derived cholesteryl esters from their sites of synthesis in subclasses of HDL to the less dense triglyceride-rich lipoproteins (33). As would be expected from the theory that net transfer is mediated by hetero-exchange of cholesteryl esters and triglycerides

(12), the net transfer of HDL cholesteryl esters occurs predominantly into the particles with the lowest cholesteryl ester/triglyceride ratio, i.e., larger or nascent VLDL and probably chylomicrons (34–36). Smaller VLDL and LDL predominantly exchange cholesteryl esters with HDL (35, 36). Since LCAT activity increases the the ratio of cholesteryl esters to triglycerides in HDL, during prolonged incubations of plasma net transfer of cholesteryl esters from HDL to VLDL is more pronounced in the presence of active LCAT (37). By contrast, initial rates of cholesteryl ester transfer are not influenced by chemical inhibition of LCAT (38). Thus, LCAT influences cholesteryl ester transfer not by a direct effect on CETP but rather as a result of alterations in lipoprotein composition.

The activity of LCAT creates a gradient of cholesterol concentration from tissues to blood components (red cells and lipoproteins), driving efflux of cholesterol into blood (33). Under the influence of CETP, cholesteryl esters synthesized by LCAT are redistributed to triglyceride-rich lipoproteins and eventually to LDL, because LDL is derived from VLDL (33). Since there are specific hepatic receptors for chylomicron remnants and for LDL (39), the redistribution of cholesteryl esters by CETP provides a mechanism for transfer of LCAT-derived cholesteryl esters from plasma to liver. Thus, the CETP-mediated cholesteryl ester transfer in plasma may represent a key step in the centripetal transport of cholesterol from peripheral tissues to liver. However, the cholesteryl ester transfer process also has the potential to cause cholesteryl ester accumulation in particles contributing to atherogenesis (see below).

The activity of CETP provides a mechanism for remodeling of LDL and HDL into smaller particles (40). In plasma, CETP activity results in an increase in LDL and HDL triglycerides at the expense of core cholesteryl esters. Since lipoprotein lipase is able (at least in vitro) to act on LDL and HDL triglycerides, the net result of sequential lipid transfer followed by lipolysis is depletion of core lipids and formation of smaller LDL and HDL particles. Because this mechanism provides a way of removing excess cholesteryl esters and forming smaller LDL, each plasma VLDL particle contains a greater number of cholesteryl ester molecules than does each LDL particle. CETP allows for remodeling of the HDL core, which is continuously being increased by the activity of LCAT. Lipid exchange is increased as a result of increases in the ratio of triglyceride-rich lipoproteins to LDL or HDL (16), explaining why hypertriglyceridemic patients have triglyceride-enriched LDL and HDL and also sometimes abnormally small LDL and HDL (41).

Sites of synthesis and regulation of CETP activity

The CETP seems to be synthesized by the perfused rabbit liver (42) and also by cultured monocyte-macrophages (43). The macrophage studies are of particular interest because some arterial wall foam cells are derived from macrophages, raising the possibility of arterial wall synthesis of CETP and a role of CETP in removal of cholesteryl esters from foam cells (43). The liver synthesis of CETP could reflect secretion by Kupffer cells. However, since the apparent mass of CETP in plasma increases rapidly in response to increased dietary fat (26), it seems likely that CETP synthesis occurs in cells directly involved in lipid flux, for example in hepatocytes or enterocytes.

Recent studies have elucidated some of the factors that may influence the activities of plasma lipid transfer proteins. In vitro lipoprotein lipase enhanced the CETP-mediated transfer of cholesteryl esters from HDL to VLDL (44). Lipase stimulation of cholesteryl ester transfer resulted from either concurrent or prior lipolysis of the lipoproteins (44). Following lipolysis of VLDL in the presence of HDL, reisolated VLDL or reisolated HDL enhanced CETP activity when reconstituted with fresh HDL or VLDL (15). The stimulatory effects resulted from modifications of the lipid composition of VLDL and HDL, particularly enrichment of VLDL with fatty acids and transfer of phospholipids and fatty acids into HDL (15). The changes in lipid composition were associated with a marked increase in the binding of CETP to both VLDL and HDL. When the enhanced binding of CETP to the lipoproteins was abolished by lowering the pH or increasing the amount of fatty acid-free albumin in the incubation medium, there was a parallel diminution in CETP-mediated transfer. Thus, lipolysis-induced alterations of the lipid composition of VLDL and HDL result in increased binding of CETP to the lipoproteins, which is responsible, at least in part, for the acceleration of cholesteryl ester transfer.

To determine whether these changes in lipoprotein lipid composition also influence physiological lipid transfer processes, we have studied the distribution and activity of CETP during alimentary lipemia. Alimentary lipemia is associated with an increase in triglyceride-rich particles, a pronounced increase in HDL phospholipid, and a small increase in plasma free fatty acids (23). There is a pronounced stimulation of cholesteryl ester transfer in incubated alimentary lipemic plasma, compared to fasting plasma (26, 45). In part this results from the increased mass of triglyceride-rich lipoproteins which favors net removal of HDL cholesteryl esters, probably as a result of cholesteryl ester-triglyceride hetero-exchange (26). In addition, during lipemia there is a pronounced redistribution of CETP, resembling that resulting from in vitro lipolysis (26). There is increased binding of CETP to larger, phospholipid-rich HDL and, in some subjects, there is also increased binding to triglyceride-rich lipoproteins. Compared to fasting HDL, HDL isolated from alimentary lipemic plasma showed increased binding of

purified CETP and also increased CETP-mediated cholesteryl ester exchange with pooled LDL. Thus, changes in HDL (probably the increased content of phospholipids and fatty acids) during alimentary lipemia resulted in increased binding and activity of CETP. A further finding to account for the stimulation of cholesteryl ester transfer during alimentary lipemia was a significant increase (1.1- to 1.8-fold in different subjects) in the apparent mass of CETP in alimentary lipemic plasma, shown by measuring the activity of CETP with pooled substrate lipoproteins in lipoprotein-free plasma (26). In summary, the increased mass of CETP and its increased binding to the lipoproteins both act to increase total CETP-mediated exchange (homo- and hetero-exchange). The increase in the total exchange of HDL cholesteryl esters combines with the increased ratio of triglyceride/cholesteryl esters in acceptor lipoproteins to produce greater net transfer of cholesteryl esters into triglyceride-rich lipoproteins. Overall, acceleration of CE transfer probably accounts for the fact that, in many subjects, especially those with high postprandial triglycerides, there is a fall in HDL cholesteryl ester mass during alimentary lipemia, despite increased activity of lecithin:cholesterol acyltransferase (46).

Species variation

There is susbstantial PTP activity in the d > 1.21 g/ml fraction of several species, e.g., humans, rats, and dogs (Tall, A. et al., unpublished results). By contrast, CETP activity varies significantly between these same species. The cholesteryl ester transfer activity has been measured in the d > 1.21 g/ml fraction of plasma from sixteen different species. High values were obtained in rabbits and trout and low values in rats and guinea pigs; humans have moderately high levels (47). In species with high levels of CETP, the cholesteryl esters are nearly equilibrated amongst the lipoproteins, while in species with low levels of CE transfer activity, such as the rat, VLDL are enriched with saturated or mono-unsaturated cholesteryl esters (reflecting origin from intestinal or hepatic ACAT), and HDL are rich in polyunsaturated fatty acids (derived from LCAT activity) (33). In dogs, swine, and rats, the LCAT-derived cholesteryl esters remain within large species of HDL and are probably catabolized with HDL, possibly in the liver (48). There is an interesting association between low levels of CETP in plasma and prominence of a large subclass of HDL called HDL-1. For example, dogs, cows, and rats, with low levels of cholesteryl ester transfer activity, have high HDL-1 (48, 49). A direct demonstration that the presence of prominent HDL-1 depends on low CETP activity is provided by experiments where CETP was injected into the rat; this resulted in reduction of the larger HDL-1 species and formation of smaller HDL (50). The species that develop high levels of apoE, cholesteryl ester-rich HDL (HDL_c) in response to an atherogenic diet (dogs, rats, and swine) also have low levels of cholesteryl ester transfer activity, while species such as monkeys, rabbits, and humans that have high levels of cholesteryl ester transfer activity do not develop prominent HDL_c on a high cholesterol diet (48). It appears that these larger HDL are formed in response to continued activity of LCAT (51) in the absence of cholesteryl ester transfer activity.

Cholesteryl ester transfer activity in hyperlipidemia and atherosclerosis

Plasma cholesteryl ester transfer may participate in the centripetal transport of cholesterol from peripheral tissues to liver. In vitro LCAT activity is inhibited by accumulation of CE within LCAT substrate lipoproteins (52). Addition of CETP results in reactivation of LCAT, as the inhibitory CE are transferred to other lipoproteins (52). Thus, the activity of CETP might regulate LCAT and the efflux of cholesterol from tissues. Fielding et al. (53) and Fielding et al. (54, 55) have reported that certain groups of patients susceptible to atherosclerosis have absent or reversed cholesteryl ester transfer between HDL and apoB,E-containing lipoproteins. The patients studied include those with familial hypercholesterolemia, dysbetalipoproteinemia, hypertriglyceridemia with atherosclerosis, and non-insulin-dependent diabetes. In the diabetic patients, the abnormality of cholesteryl ester transfer was associated with an increased cholesterol/phospholipid ratio of VLDL and LDL and net uptake of plasma cholesterol (due to increased influx) when the abnormal but not normal plasma was incubated with fibroblasts (55). The abnormalities of cholesteryl ester transfer were thought to reflect abnormal properties of acceptor apoB-containing particles. These studies suggest the possibility that certain patients susceptible to atherosclerosis have abnormal centripetal cholesterol transport due to a defective transfer of cholesteryl esters in plasma, as well as a tendency to deposit cholesterol in tissues due to an increased cholesterol/phospholipid ratio in their lipoproteins.

However, other evidence suggests that a reverse cholesterol transport system, comprising HDL, LCAT, and CETP, may not ordinarily regulate the levels of cholesterol in tissues. Although Miller and Miller (56) reported an inverse correlation between HDL levels and tissue cholesterol pool sizes, a more definitive analysis of a larger group of patients has shown that HDL does not have a statistically independent relationship with tissue cholesterol pools (57). Although HDL and LCAT may promote cholesterol efflux from cultured cells, a variety of different particles, including erythrocytes, are effective acceptors of macrophage cholesteryl esters, and efflux of macrophage cholesterol does not require active LCAT (58).

In fact, CETP activity may contribute to the development of atherosclerosis by causing transfer of newly syn-

thesized plasma cholesteryl esters to particles that deposit cholesteryl esters in tissues. Species that lack cholesteryl ester transfer activity in plasma are relatively resistant to dietary atherosclerosis, while those that have active cholesteryl ester transfer (rabbits, monkeys, and humans) develop dietary atherosclerosis more readily. In recent studies of the cholesterol-fed rabbit, we have found that there are two- to threefold increased levels of CETP in plasma, and that this is accompanied by enhanced cholesteryl ester transfer from HDL to apoB-containing particles. The cholesteryl ester-enriched apoB-lipoproteins caused accumulation of large amounts of cholesteryl esters in cultured macrophages (Tall, A., et al., unpublished results). Our preliminary studies also indicate that some hyperlipidemic patients with low levels of HDL cholesteryl esters have an increased mass of CETP in plasma and accelerated transfer of cholesteryl esters from HDL to apoB-containing lipoproteins. These considerations emphasize the pro-atherogenic potential of the cholesteryl ester transfer process and lead to the following speculations.

In subjects with high HDL cholesterol levels, there may be low rates of cholesteryl ester transfer from HDL to apoB containing lipoproteins (**Fig. 1A**). The high levels of HDL cholesteryl esters may, in part, reflect the slow rate of transfer to apoB-containing lipoproteins. These subjects probably have an alternate, less efficient mechanism for disposing of HDL cholesterol or cholesteryl esters in the liver or in other tissues. That such an alternative disposal route exists is suggested by the fact that, in human plasma, the rate of new cholesteryl ester formation exceeds the rate of net cholesteryl ester transfer from HDL to other particles (26, 45). Also, species that lack cholesteryl ester transfer activity must have another mechanism for disposing of HDL cholesteryl esters, such as the uptake of apoE-containing HDL in the liver (48).

On the other hand, subjects with low HDL cholesterol levels may have high rates of cholesteryl ester transfer from HDL to apoB-containing lipoproteins (Fig. 1B). The low level of HDL cholesteryl esters may result in part from the accelerated cholesteryl ester transfer. The increased rate of cholesteryl ester transfer could result from higher levels of apoB-containing lipoproteins as a result of increased production or decreased clearance (for example, from low lipoprotein lipase activity or low levels of hepatic LDL receptors). These subjects may also have impaired clearance of chylomicrons during alimentary lipemia, and

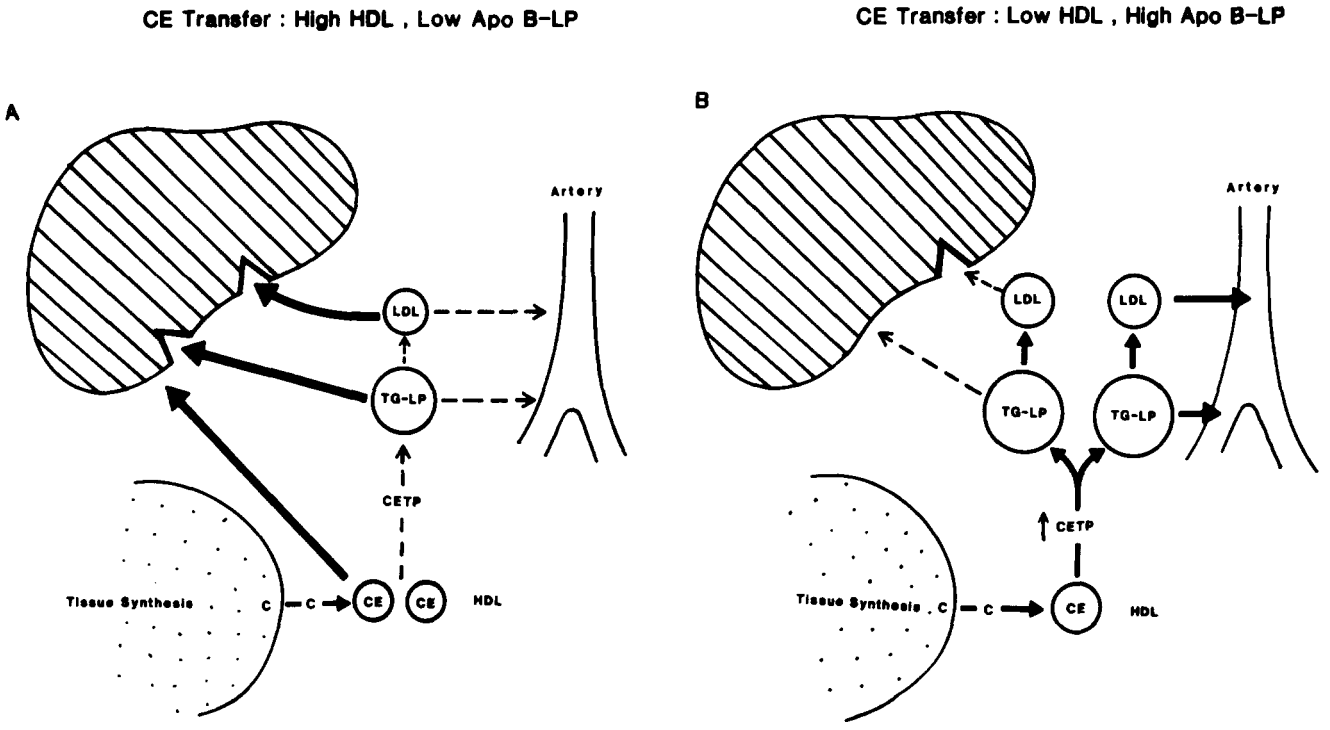

Fig. 1. A: Possible cholesteryl ester transfer mechanisms in subjects with high HDL and low levels of apoB-containing lipoproteins. Cholesterol diffuses from the tissues into HDL and is esterified by LCAT. Cholesteryl ester (CE) transfer from HDL to apoB-lipoproteins is slow because of a low mass of acceptor particles (triglyceride-rich lipoproteins, TG-LP) and of CETP. There may be an alternate mechanism to dispose of HDL cholesteryl esters in the liver. It is possible that CETP may directly influence the movement of cholesteryl esters between lipoproteins and tissue, for example, the uptake of HDL cholesteryl esters by liver. B: Potential cholesteryl ester transfer mechanisms in subjects with low HDL and high levels of apoB-containing lipoproteins. Cholesteryl ester (CE) transfer from HDL to apoB-containing lipoproteins is accelerated because of the increased mass of acceptor particles and of CETP. The mass of apoB-lipoproteins may be increased due to overproduction or decreased clearance or defective lipolysis. CE accumulating in apoB-lipoproteins (chylomicron and VLDL remnants and LDL) contributes to deposition of cholesterol in the arterial wall.

a more pronounced fall in HDL cholesteryl esters during lipemia (46, 59). In this analysis, the cholesteryl ester transfer is increased secondary to altered metabolism of apoB-containing lipoproteins. However, the plasma levels of CETP may be increased and the CETP provides a link between increased amounts of atherogenic remnant lipoproteins or LDL and decreased levels of HDL cholesterol (60, 61). It is also possible that, in some individuals, increased levels of CETP or changes in the activity of CETP, for example as a result of altered binding to the lipoproteins, may play a primary role in determining low levels of HDL cholesterol.

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