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Commentary

Cholesteryl ester transfer protein facilitates the movement of water-insoluble drugs between lipoproteins: a novel biological function for a well-characterized lipid transfer protein

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Abstract

This review article addresses the recently discovered finding that cholesteryl ester transfer protein (CETP) can facilitate the transfer of water-insoluble drugs between different lipoprotein subclasses. This protein, which is often referred to as lipid transfer protein I (LTP I), is involved in the lipid regulation of lipoproteins. It is responsible for the facilitated transfer of core lipoprotein lipids, cholesteryl ester and triglycerides, and approximately one-third of the coat lipoprotein lipid, phosphatidylcholine, between different plasma lipoproteins. The human body appears to recognize exogenous water-insoluble drugs as lipid-like particles, which suggests that these compounds may interact with lipoproteins just like endogenous plasma lipids, and thus their transfer between lipoproteins may be facilitated by plasma CETP. Patients with a variety of diseases (i.e. diabetes, cancer, AIDS) often exhibit hypo- and/or hypercholesterolemia and triglyceridemia, commonly referred to as dyslipidemias, which result in changes in their plasma lipoprotein-lipid composition and concentration. The interaction of water-insoluble drugs with these dyslipidemic lipoproteins may be responsible for the differences seen in the pharmacokinetics and pharmacodynamics of the drug within different diseased patient populations. It is possible that these differences may be linked to the ability of CETP to transfer these compounds from one lipoprotein to another. This review examines the current understanding of the relationship between CETP activity and the lipoprotein distribution of a number of compounds (e.g. amphotericin B and cyclosporine A). It further suggests that additional research will expand our understanding of the role of CETP to explain other functions in lipophilic drug distribution and metabolism.

Keywords: Cholesteryl ester transfer protein; Lipid transfer protein I; Cyclosporine A; Amphotericin B; Drug movement and lipoproteins

1. Introduction

Lipoproteins, commonly involved in the transport of lipids throughout the bloodstream, appear to have a wider biological role than simply the movement of water-soluble lipids from the systemic circulation to tissues [1]. The lipoproteins are also involved in the binding and subsequent transport of a number of water-insoluble compounds, including AmpB and CSA [1]. Current research further suggests that changes in the lipoprotein binding of drug compounds may have a major impact on the efficacy and safety of the aforementioned compounds, particularly since they are often administered to patients with abnormal lipid metabolism (hypo/hypercholesterolemia and/or hypertriglyceridemia). In this review article, we present evidence to suggest that one of the characteristics of aberrant lipid metabolism, namely changes in the rate of facilitated transfer of CE and TG between different lipoprotein classes, mediated by the glycoprotein CETP [2], may be responsible for altering the association of these compounds with specific plasma lipoproteins and thus modify their pharmacokinetics and pharmacodynamics. Specifically, this article addresses the recently discovered finding that CETP can facilitate the transfer of several water-insoluble drugs between different lipoprotein subclasses.

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Abbreviations: AmpB, amphotericin B; ApoB, apolipoprotein B; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; CSA, cyclosporine A; DMPC, dimyristoylphosphatidylcholine; DMPG, dimyristoylphosphatidylglycerol; HDL, high-density lipoproteins; LDL, low-density lipoproteins; LTP I, lipid transfer protein I; PLTP, phospholipid transfer protein; SA, stearylamine; TG, triglyceride; TP2, monoclonal antibody directed against CETP; VLDL, very-low-density lipoproteins.

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2. CETP

CETP (often referred to as lipid transfer protein I [LTP I]) is a 476 amino acid hydrophobic glycoprotein with a molecular mass of 74 kDa [3]. CETP and PLTP, believed to have evolved from a common ancestor, belong to the family of lipopolysaccharide binding proteins [4]. The two proteins share 20% homology and have regions homologous to those of lipopolysaccharide binding proteins [4]. CETP expression between mammalian species is variable, with undetectable levels in rats and mice, moderate levels in humans, and high levels in rabbits [5]. The majority of CETP in humans is synthesized in the liver, with lower levels produced in the adipose tissue, kidneys, heart, and spleen [6].

CETP facilitates the transfer of cholesteryl esters from HDL to ApoB-containing lipoproteins (VLDL and LDL) with a reciprocal transfer of TG [2,7]. CETP, along with PLTP, plays an important role in the metabolism and remodeling of plasma lipoproteins [8]. CETP may also play a role in certain disease processes such as atherosclerosis by redistributing cholesterol from the anti-atherogenic HDL particles to the pro-atherogenic LDL particles. Conversely, CETP is also implicated in the process of reverse cholesterol transport, which removes cholesterol from peripheral tissues and is viewed as anti-atherogenic. The exact role of CETP in the development of atherosclerosis remains uncertain and is the subject of various studies [6].

CETP is regulated by cholesterol, with an increase in activity and expression seen in response to cholesterol [9]. In studies using human-CETP transgenic mice it was determined that the increased activity could be attributed to an increase in transcription of the *CETP* gene [10]. Conversely, CETP activity has been reduced in response to corticosteroids and lipopolysaccharides [11].

The CETP binding domain for neutral lipids (CE and TG) is located in the 26 amino acid residues that comprise the carboxyl-terminal end of CETP [12]. This was shown by the use of monoclonal antibodies raised up against CETP, which blocks this binding domain and prevents the CETP-mediated transfer of neutral lipid between HDL and ApoB-rich lipoproteins [13]. The domain is apparently comprised of an amphipathic helix, which consists of a charged/polar residue face and a hydrophobic residue face to which binding of neutral lipid occurs [14]. This binding of neutral lipids may induce a conformational change in the protein, which enhances its binding to lipoproteins [12]. Furthermore, recent studies by our group have suggested that water-insoluble drugs themselves may bind to this site [15–17].

CETP forms complexes with VLDL, LDL, and HDL, with the complex of CETP and HDL being the most stable one [18]. In plasma, CETP is recovered mainly in the HDL fraction. The binding of CETP to lipoproteins is due to an electrostatic interaction between positively charged regions of CETP with negatively charged components on the lipoprotein [19]. The stability of the lipoprotein–CETP complex is enhanced as the negative charge density of the lipoprotein is increased [20]. It has been shown that there is an optimal affinity of CETP for both the donor and acceptor molecule in order to obtain maximal lipid transfer activity [20]. Thus, changes in lipoprotein distribution and composition as a result of disease state, diet, or drug therapy could affect lipid transfer rates.

CETP-facilitated lipid transfer has been proposed to occur by two methods: (a) a carrier-mediated process [21] in which CETP acts as a shuttle between the donor and acceptor molecule, and (b) a ternary mechanism [22] in which a donor–CETP complex collides with the acceptor, forming a ternary complex. In the carrier-mediated process, CETP binds to the donor molecule (HDL), which may result in a conformational change, exposing a neutral lipid-binding site on CETP. A CE molecule is located to the binding site, and CETP dissociates from the HDL. The CETP–CE complex then diffuses and eventually binds to an acceptor molecule (VLDL or LDL) and the CE is exchanged for a molecule of triacylglycerol. The CETP dissociates from the receptor molecule, and the process repeats.

In the ternary mechanism of lipid exchange, the CETP–HDL complex does not dissociate. Instead, this complex will collide and bind to the acceptor molecule forming a ternary complex. Exchange of a cholesteryl ester for a triacylglycerol is then facilitated by CETP. Once the exchange of neutral lipids is completed, the three components dissociate, and the process starts over.

Many studies into the mechanism of lipid transfer have been performed to determine whether the shuttling or the collision mechanism predominates in humans. From these studies it is generally accepted that both mechanisms most likely coexist *in vivo* and play a role in the transfer of neutral lipids among lipoproteins [23].

Since the human body may recognize water-insoluble compounds as lipid-like particles, we have hypothesized that an elevation in CETP concentration may increase the transfer of drugs including AmpB [24], halofantrine [25], and CSA [15–17] between different lipoprotein classes. Evidence to support this hypothesis with two well-known drugs, AmpB and CSA, is presented in the subsequent paragraphs.

3. CETP and AmpB

Despite the development of a number of new lipid-based anti-fungal formulations [26], AmpB, formulated as a colloidal suspension, remains one of the most effective and affordable agents in the treatment of systemic fungal infections [27]. However, the clinical use of AmpB has been limited by dose-dependent renal toxicity [26,27].

Several lines of evidence indicate that the association of AmpB with serum LDL is regulated by an increase in CETP plasma concentration and activity and is involved in the development of AmpB-induced kidney toxicity [24].

Table 1
Effect of CETP on the distribution of AmpB and ABLC into serum lipoproteins after a 60 min incubation in pooled human serum

Lipoprotein fraction (%)	AmpB		ABLC	
	No CETP (%)[a]	CETP added[b] (%)[a]	No CETP (%)[a]	CETP added[b] (%)[a]
HDL	74 ± 0.5	48.6 ± 4.9[*]	92.0 ± 5.0	88.9 ± 5.4
LDL	22 ± 5.5	45.6 ± 4.4[*]	Not detected	9.0 ± 7.8

Abbreviations: CETP, cholesteryl ester transfer protein; AmpB, amphotericin B; ABLC, amphotericin B–lipid complex; HDL, high-density lipoproteins; and LDL, low-density lipoproteins. Values are means ± SD, N = 6. Adapted, with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc., from J Pharm Sci 1994;83:1006–10. Copyright (1994) American Chemical Society and the American Pharmaceutical Association [24].

[a] Percent of initial AmpB incubated.

[b] 0.64 μg protein/mL was added to serum having an endogenous CETP concentration of 12 μg protein/mL.

[*] $P < 0.05$ vs AmpB with no CETP added.

However, when AmpB is incorporated into non-toxic phospholipids to form an AmpB–lipid complex (ABLC), AmpB binding to serum LDL decreases [28] and AmpB-induced kidney toxicity is reduced significantly [29].

When AmpB was incubated in human serum for 1 hr at 37°, over 70% of the drug was found bound with serum HDL [28]. However, preliminary findings suggest that an increase in CETP concentration increases the binding of AmpB with serum LDL (Table 1). This observation suggests that changes in CETP concentration may regulate the distribution of AmpB among the HDL and LDL fractions of human serum. This observation was supported recently by Pato *et al.* [30], who reported that AmpB was shown to form a complex with plant lipid transfer protein I, although no binding affinity could be determined.

However, the increase in the concentration of CETP did not increase the binding of AmpB with serum LDL when ABLC was incubated in human serum (Table 1) [24]. Furthermore, the presence of empty or AmpB-containing lipid complexes decreased the ability of CETP to transfer CE from HDL to LDL (Fig. 1A) [24]. These observations suggest that the presence of lipid complexes in serum results in the reduction of CETP-mediated transfer of CE from HDL to LDL (Fig. 1B). Since AmpB binds to unesterified and esterified cholesterol in serum [1], this finding may explain in part the decreased association of AmpB with serum LDL when formulated into these lipid complexes.

4. CETP and CSA

CSA is an effective immunosuppressant used in the treatment of a number of autoimmune diseases as well as in human transplantation [31,32]. In addition, CSA has been shown to bind with lipoproteins upon incubation in human plasma [33–35]. We have further shown that changes in the total and plasma lipoprotein lipid concentration and composition influence the lipoprotein binding of CSA [36]. One of the proposed biological consequences of CSA binding to lipoproteins is the decrease in the pharmacological effect of the drug. Several investigators have reported decreased pharmacological effects of CSA with hyperlipidemia (particularly in hypertriglyceridemia) [37,38], and increased toxic effects of CSA with hypolipidemia (particularly hypocholesterolemia) [39].

Investigations have demonstrated that the cellular uptake of CSA is mediated through HDL [40] and LDL receptors [41], although recent work has shown that lipoproteins may not serve as a vehicle for the cellular uptake of CSA into hepatic-derived cells [42]. However, Lemaire *et al.* [43] have suggested that the availability of the drug to tissue and, hence, its pharmacological (or toxic) effects may depend upon the lipoprotein to which the drug is bound. They have observed an enhanced antiproliferative effect of CSA when it was bound to LDL, which was not evident when the drug was bound to either VLDL or HDL [43]. Furthermore, transplantation patients, many of whom are administered CSA, exhibit plasma dyslipidemias (i.e. lipid disturbances) including hypocholesterolemia and hypertriglyceridemia [44]. In addition, these dyslipidemic plasmas have an elevated CETP concentration [6]. Thus, determining if CETP facilitates the binding of CSA to certain lipoproteins may help to explain the differences in the pharmacological behavior of CSA following administration to hypocholesterolemic [39] and/or hypertriglyceridemic patients [37,38].

Therefore, the objectives of the investigations presented below [15] were to determine if CETP regulates the plasma lipoprotein distribution of CSA and by what mechanisms. We hypothesized that the transfer of CSA between HDL and LDL was a result of direct movement of CSA and/or the co-transport of CSA and CE by CETP. Experimental strategies that involved the supplementation and inhibition of CETP were used to test these hypotheses.

In experiments that were designed to directly measure the potential role of CETP in facilitating CSA transfer, CETP-mediated percent transfer of CE among HDL and LDL particles was significantly different from that of CSA (Fig. 2). The differences in the percent transfer of CE versus CSA may be attributed to the ability of CETP to transfer lipid and drug separately. Furthermore, differences could be attributed to the ability of HDL and LDL particles to accumulate a higher amount of CE than CSA (e.g. HDL sequesters approximately 1460 ng CE/ng CSA; LDL sequesters approximately 3564 ng CE/ng CSA). Our findings further suggest that HDL particles are much more effective than LDL particles at binding CSA [15].

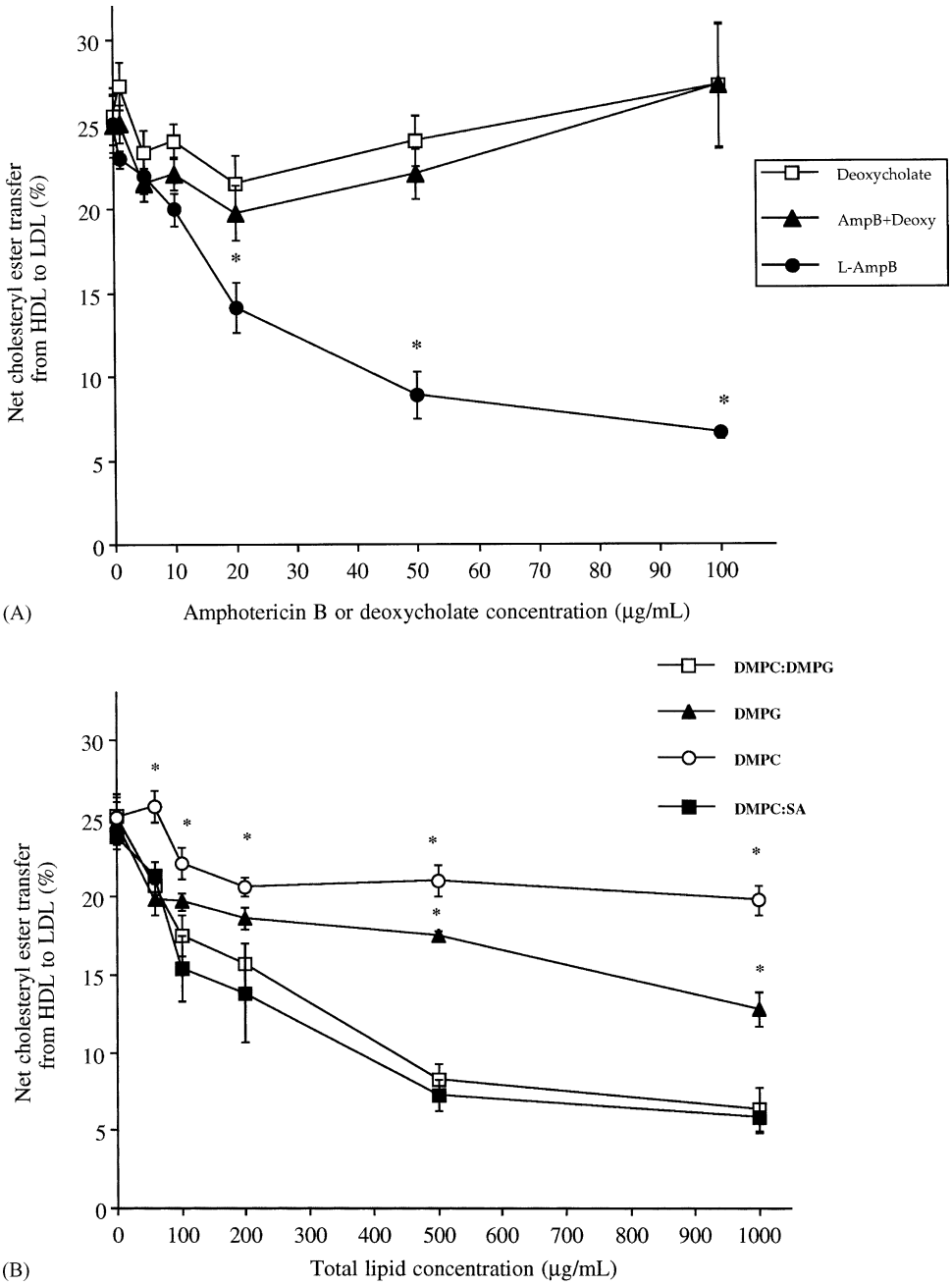
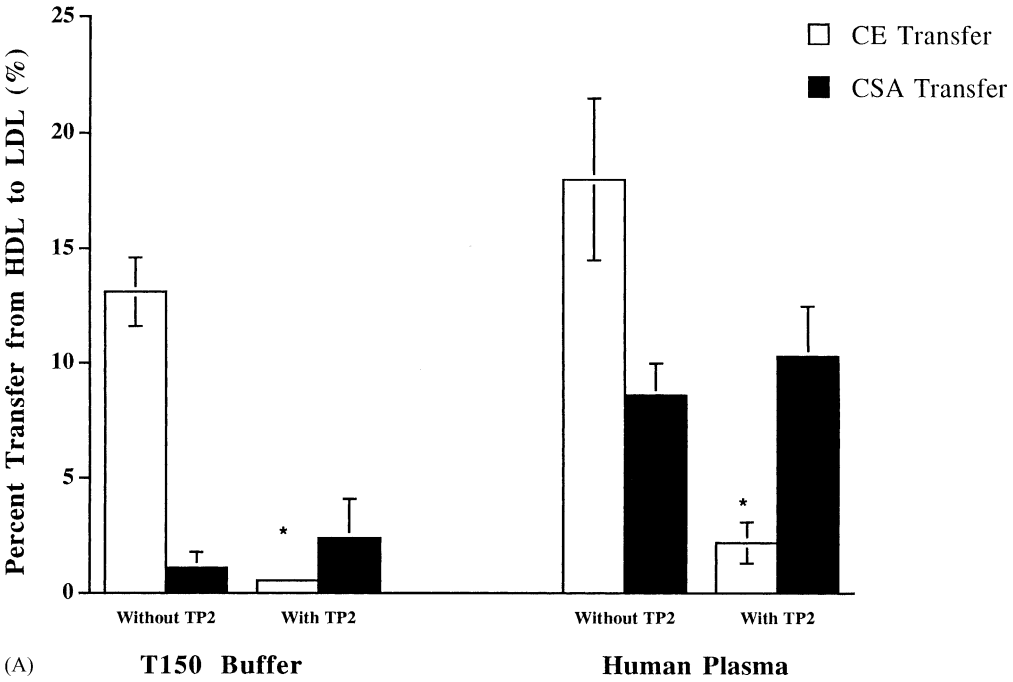


Fig. 1. (A) Effects of AmpB, deoxycholate, and ABLC on CE transfer activity. AmpB + deoxycholate (▲, 1–100 μg/mL of AmpB), deoxycholate, (□, 1–100 μg/mL of deoxycholate), and ABLC (L-AmpB) (●, 1–100 μg/mL of AmpB) were incubated for 120 min at 37° in delipidated human serum that contained [^{3}H]cholesterol oleate-HDL, unlabeled LDL (in a 1:1 ratio based on apoprotein concentration), and excess CETP (0.64 μg protein/mL). Net CE transfer from HDL to LDL was determined and compared with controls that contained no drug or lipid-complex treatment. Data are presented as means ± SD (N = 4). Key: (∗) $P < 0.05$ vs net CE transfer control. (B) Effect of liposomal-lipid charge on CETP-mediated CE transfer activity. Net percent transfer of CE from HDL to LDL at 37° for 120 min in delipidated human serum containing [^{3}H]cholesterol oleate-HDL, unlabeled LDL (in a 1:1 ratio based on apoprotein concentration), and excess CETP (0.64 μg protein/mL) in the presence of empty liposomes of DMPC plus DMPG (□), DMPG alone (▲), DMPC alone (○), and DMPC plus SA (■) (1–1000 μg/mL of total lipid). Data are presented as means ± SD (N = 3). Key: (∗) $P < 0.05$ vs net CE transfer at 0 μg/mL of total lipid. Panels A and B are adapted, with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc., from J Pharm Sci 1994;83:1006–10. Copyright (1994) American Chemical Society and the American Pharmaceutical Association [24].

Sgoutas *et al.* [35] have proposed that the nature of CSA's association with HDL and LDL particles appears to be non-specific and of low affinity and high capacity, suggesting that CSA is physically dissolved within the lipoprotein-lipid component. Furthermore, since CSA appears to be only partially recognized by CETP as an endogenous lipid compound, the ability of CETP to transfer CSA between HDL and LDL is only part of the story. This is supported by evidence that demonstrates that the percent transfer of CSA from LDL to HDL is significantly greater in human plasma than in T150 buffer (Fig. 2B), regardless of whether CETP activity was decreased or not.



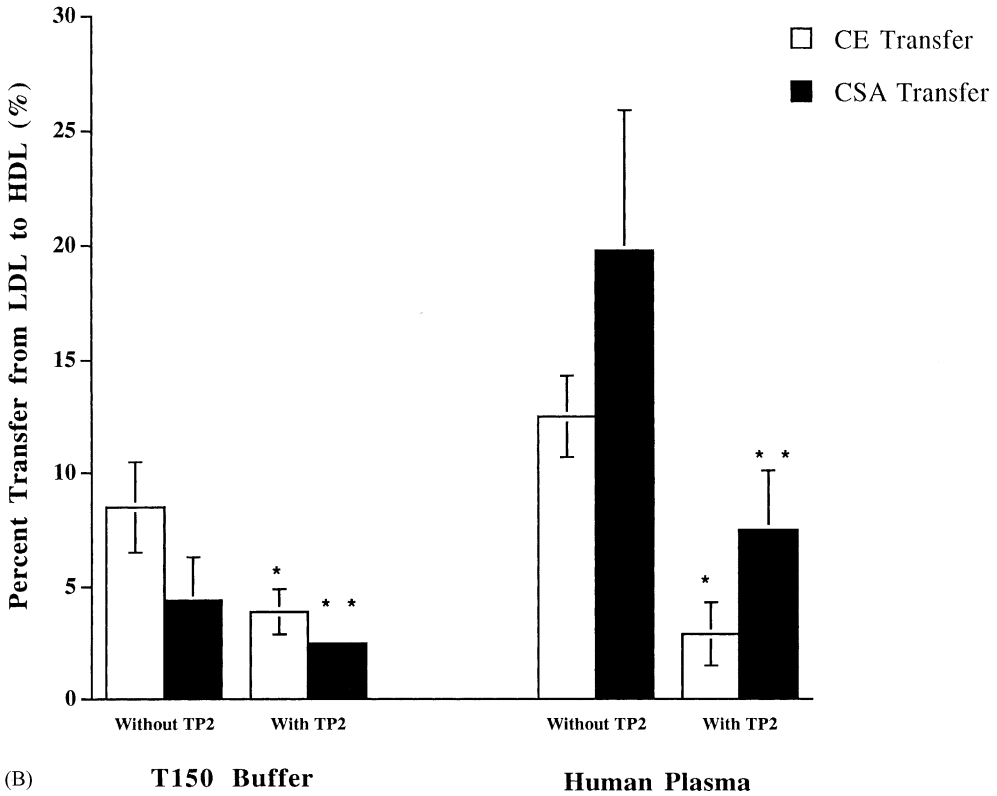


Fig. 2. (A) CE and CSA percent transfer from HDL to LDL, in the presence or absence of a monoclonal antibody (TP2) directed against CETP, following the incubation of radiolabeled CE- and CSA-enriched HDL with unlabeled LDL (at 10 μg lipoprotein cholesterol) for 60 min at 37° in T150 buffer that was supplemented with CETP (1.0 μg protein/mL) or delipidated human plasma that contained 1.0 μg protein/mL of CETP. Data are expressed as means ± SD (N = 6). Key: (∗) $P < 0.05$ vs CE percent transfer without TP2. (B) CE and CSA percent transfer from LDL to HDL, in the presence or absence of a monoclonal antibody (TP2) directed against CETP, following the incubation of radiolabeled CE- and CSA-enriched LDL with unlabeled HDL (at 10 μg lipoprotein cholesterol) for 60 min at 37° in T150 buffer that had been supplemented with CETP (1.0 μg protein/mL) or delipidated human plasma that contained 1.0 μg protein/mL of CETP. Data are expressed as means ± SD (N = 6). Key: (∗) $P < 0.05$ vs CE percent transfer without TP2; and (∗∗) $P < 0.05$ vs CSA percent transfer without TP2. Panels A and B are adapted, with permission, from J Pharmacol Exp Ther 1998;284:599–605. Copyright (1998) The American Society for Pharmacology and Experimental Therapeutics [15].

These findings suggest two possibilities: (a) the spontaneous transfer of CSA, and/or (b) the facilitated transfer of CSA by other endogenous plasma factors (e.g. TG and phospholipid transfer proteins) [16,17]. However, the percent transfer of CSA from HDL to LDL, although significantly greater in human plasma than in T150 buffer(Fig. 2A), did not decrease when a significant reduction in CETP-mediated CE transfer was observed. These findings further support the notion that the transfer of CSA from HDL to LDL is not CETP-mediated and may be due to spontaneous and/or facilitated transfer by other endogenous plasma factors. In addition, these results suggest that CETP may be only partially responsible for the greater capacity of HDL than LDL to accept CSA. Different physical–chemical characteristics of HDLs including lipid composition and overall particle charge may possibly explain the preference of CSA to bind with HDL. Studies that investigate these characteristics are currently being completed in our laboratory.

When the molar transfer rates of CE were calculated, a number of additional conclusions could be made. The CE molar transfer rate between HDL and LDL was not significantly different in human plasma versus T150 buffer. However, the percent transfer of CSA from HDL to LDL and LDL to HDL was 5–9 times greater, respectively, in human plasma than in T150 buffer (Fig. 2). These observations provide further evidence that CSA transfer is independent of CE transfer and is mediated by plasma factors other than CETP. Furthermore, when CETP-mediated transfer of CE between HDL and LDL was inhibited by TP2, only the transfer of CSA from LDL to HDL was decreased significantly. These results suggest that the transfer of CSA from LDL to HDL is partially facilitated by CETP; however, the transfer of CSA from HDL to LDL is not facilitated by CETP but by other plasma factors and/or spontaneous transfer [15]. Subsequent studies were published to suggest that CETP-mediated transfer of triglycerides, but not phospholipids, regulates the transfer of CSA between lipoproteins [16,17].

In conclusion we have determined that the distribution of CSA among lipoproteins is partially influenced by CETP. Since many bone marrow transplantation patients exhibit lipid disturbances, including hypocholesterolemia and hypertriglyceridemia, these results may provide an explanation for the unpredictable and inconsistent pharmacokinetics and pharmacodynamics of CSA following administration. Taken together, these studies suggest that further work aimed at developing applications in CETP-mediated transport and controlled release of low molecular weight drugs is warranted.

5. Biological implications and future studies

In the present review, the recently discovered finding that CETP can facilitate the transfer of water-insoluble drugs between different lipoprotein subclasses suggests that this protein may have potential application in the field of drug delivery. One such example of this is found in the recent paper by Pato *et al.* [30]. This group reported that skin lipids, such as sphingosine, sphingomyelin, and cerebroside, BD56 (an azole derivative that has antitumoral and/or antileishmania properties), and AmpB were shown to bind to plant lipid transfer protein I, suggesting a potential application of plant lipid transfer proteins for drug delivery. In addition, Kostner *et al.* [45] reported that human plasma phospholipid transfer protein accelerates the exchange and/or transfer of α-tocopherol between plasma lipoproteins and cells.

The work presented represents a prerequisite for further studies including *in vitro* and *in vivo* testing of complexes between various drugs and CETP. Moreover, this protein exhibits a transfer activity that should make its use attractive when drugs have to penetrate lipid membranes.

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