Effect of Inhibiting Cholesteryl Ester Transfer Protein on the Kinetics of High-Density Lipoprotein Cholesteryl Ester Transport in Plasma
In Vivo Studies in Rabbits


Objective—Inhibitors of cholesteryl ester transfer protein (CETP) have been developed as potential anti-atherogenic agents. Theoretically, however, they may be pro-atherogenic by blocking one of the pathways for removing high-density lipoprotein (HDL) cholesteryl esters (CE) from plasma in the final step of reverse cholesterol transport. Here we describe how CETP inhibition in rabbits impacts on the kinetics of HDL CE transport in plasma.

Methods and Results—Administration of a CETP inhibitor reduced CETP activity by 80% to 90% and doubled the HDL cholesteryl ester concentration. Multi-compartmental analysis was used to determine HDL CE kinetics in CETP-inhibited and control rabbits after injection of tracer amounts of both native and reconstituted HDL labeled with $^3$H in the CE moiety. In control rabbits, HDL CE was removed from plasma by both a direct pathway and an indirect pathway after transfer of HDL CE to the very-low-density lipoprotein/low-density lipoprotein fraction. In CETP-inhibited rabbits there was an almost complete block in removal via the indirect pathway. This did not compromise the overall removal of HDL CE from plasma, which was not different in control and inhibited animals.

Conclusion—Inhibiting CETP in rabbits does not compromise the removal of HDL CE from plasma. (Arterioscler Thromb Vasc Biol. 2006;26:884-890.)

Key Words: cholesteryl esters ■ high-density lipoprotein ■ inhibitor ■ kinetics ■ reverse cholesterol transport

Drugs that inhibit activity of the cholesteryl ester transfer protein (CETP) are currently being evaluated as potential anti-atherogenic agents in humans. The proposition that CETP may be pro-atherogenic and that its inhibition may be anti-atherogenic has been supported by a number of animal studies in which the transfer protein has either been overexpressed in rodents or inhibited in rabbits. There are, however, studies that do not support this proposition. For example, overexpression of CETP in hypertriglycerideremic mice and in mice engineered to overexpress lecithin:choles- terol acyltransferase (LCAT) has been reported to be anti- rather than pro-atherogenic. And in one study of markedly hypercholesterolemic rabbits with severe atherosclerosis, inhibition of CETP had no effect on the extent of atherosclerosis. There have also been inconsistencies in the evidence collected from studies of CETP-deficient humans. Some reports have suggested that CETP deficiency is associated with a reduced incidence of atherosclerotic disease, whereas others have suggested that atherosclerosis may be increased in CETP-deficient subjects. These inconsistencies have fuelled an ongoing debate about the therapeutic potential of drugs designed to inhibit CETP in humans.

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Inhibiting CETP decreases the transfer of cholesteryl esters (CE) from high-density lipoproteins (HDL) to very-low-density lipoproteins (VLDL) and low-density lipoproteins (LDL). This results in an increase in the concentration of the protective HDL fraction while reducing the CE content of the pro-atherogenic VLDL/LDL fraction. However, it has also been argued that inhibiting CETP has the potential to increase rather than decrease the development of atherosclerosis by compromising reverse cholesterol transport, the pathway in which cholesterol in peripheral tissues is transported to the liver for elimination in bile. This pathway involves an initial uptake of cell cholesterol by HDL, where it is esterified by LCAT. The HDL CE is subsequently delivered to the liver by direct and indirect pathways. The direct pathway appears to be mediated by the scavenger receptor B1 (SR-B1), whereas the indirect pathway involves the CETP-mediated...
transfer of cholesteryl esters from HDL to the VLDL/LDL fraction, with delivery to the liver being accomplished via the LDL receptor pathway. By definition, this indirect pathway will be reduced if activity of CETP is inhibited.

The question arises, will a reduction in the indirect pathway associated with inhibition of CETP compromise the overall removal of HDL CE from plasma?

This issue is addressed in the current study in which we investigate the impact of inhibiting CETP in vivo in rabbits on the kinetics of HDL CE transport. We report that the reduction in the indirect pathway that occurs when CETP is inhibited does not compromise the overall removal of HDL CE from plasma.

**Methods**

Male New Zealand White rabbits weighing ~3 kg were used. For the studies using radiolabeled reconstituted HDL (rHDL) as a tracer to measure HDL CE kinetics, rabbits were obtained from the Institute of Medical and Veterinary Science, Adelaide, Australia. Procedures for these studies were approved by the Institute of Medical and Veterinary Science Animal Ethics Committee. For the studies using radiolabeled native HDL as a tracer, rabbits were obtained from Marungora Stud, Wauchope, New South Wales. Procedures for these studies were approved by the Sydney South West Area Health Service Animal Welfare Committee.

All rabbits were maintained on a normal chow diet. The oral CETP inhibitor, CP-456,643, was provided by Pfizer Inc (Groton, Conn). This CETP inhibitor is structurally similar to torcetrapib and appears, like torcetrapib, to act by enhancing the association of CETP for its lipoprotein substrates, thereby creating a nonproductive complex and reducing the activity of CETP in plasma. A stock solution of CP-456,643 in chloroform (600 mg/mL) was prepared. Rabbit chow was mixed with CP-456,643 and the solvent evaporated in a fume hood overnight. The supplemented chow contained 5 mg/kg of CP-456,643. Control rabbits were maintained on a diet of normal chow. Having established that 4 days of treatment with CP-456,643 was sufficient to achieve maximal inhibition of CETP activity and maximal elevation of HDL CE concentration, the treated rabbits received the supplemented chow for 5 days before the kinetic studies were performed. Blood samples were taken for lipid analysis and quantification of CETP activity from both untreated rabbits and from CETP inhibitor (CETPi)-treated rabbits on day 5 after CP-456,643 administration.

**Preparation of HDL Containing [3H]-Labeled CE**

**Spherical Reconstituted HDL**

HDL (1.07<d<1.21 g/mL) were isolated from rabbit plasma by sequential ultracentrifugation. Apolipoprotein (apo) A-I was isolated from the HDL by delipidation followed by chromatography on a Q Sepharose Fast Flow column (Pharmacia Biotech AB). The purity of apoA-I was confirmed by SDS-PAGE (Phast System). LCAT was isolated from samples of pooled human plasma as described.14,15 Discoidal rHDL containing [3H]FC were prepared using the cholate dialysis method.16 The rHDL contained 1-palmitoyl-2-linoleoylphosphatidylcholine (PLPC), unlabeled free cholesterol (FC), a tracer amount of [1α,2α(3H)] cholesteryl ([3H]FC) (Amersham Pharmacia Biotech), and apoA-I. Once formed, the discoidal rHDL were dialyzed against 5×1 L of Tris-buffered saline (TBS) (pH 7.4) containing 0.15 mol/L NaCl, 0.005% (wt/v) EDTA-Na2, and 0.006% (wt/v) NaN3 before use. The molar ratio of PC/FC/phosphatidylcholine:cholesteryl oleate in these particles was 900:1. These samples were collected into tubes containing 0.1 mg/mL EDTA-Na2 and 2 mmol/L of 5,5'-dithiobis(nitrobenzoic acid) (DTNB) and kept on ice until being further processed.

**Native HDL**

Native HDL (1.07<d<1.21 g/mL) were isolated from the plasma of rabbits that were either untreated or had received the oral CETP inhibitor for 5 days. The isolated HDL were labeled with [3H]-cholesteryl oleate ([1α,2α(H)]CO; Sigma) by exchange from donor particles using purified human plasma CETP.19 The donor particles were prepared by sonication of egg phosphatidylcholine and cholesteryl oleate supplemented with [1α,2α(H)]CO (300 μCi). The molar ratio of phosphatidylcholine:cholesteryl oleate in these particles was 900:1. The donor particles and native HDL were subsequently incubated for 6 hours at 37°C in the presence of purified human CETP. The molar ratio of HDL protein:donor particle phospholipid was 18:1. After the exchange, the donor particles were separated from HDL by ultracentrifugation at a density of 1.07 g/mL. The fraction of d=1.07 g/mL were isolated as the supernatant following ultracentrifugation at a density of 1.21 g/mL. The isolated preparations of ([1α,2α(H)]CO)-HDL were dialyzed extensively against endotoxin-free phosphate-buffered saline (3×1 L) before use. The specific radioactivity of the CE in these preparations of native HDL was 5 to 12×106 cpm/μmol cholesteryl ester.

**In Vivo Studies**

Spherical rHDL containing 3×108 cpm of [3H]-labeled CE or native HDL containing 3.0×108 cpm of [3H]-labeled CE were injected into the left marginal ear vein of recipient rabbits. Blood samples were drawn from the right central ear artery at serial intervals up to 6 hours after injection of the tracer. These samples were collected into tubes containing 0.1 mg/mL EDTA-Na2 and 2 mmol/L of 5,5'-dithiobis(nitrobenzoic acid) (DTNB) and kept on ice until being further processed.

**Sample Preparation and Analysis**

Plasma was isolated by centrifugation at 3000 rpm for 15 minutes at 4°C. In the studies using labeled rHDL as tracer, the VLDL/LDL fraction was separated from HDL by precipitation with an equal volume of heparin and MnCl2 (2500 IU/mL heparin/1 mol/L MnCl2). It was established that no apoA-I was precipitated by this procedure. In the studies using the labeled native HDL as tracer, the VLDL/LDL fraction was separated from the HDL by ultracentrifugation at a density of 1.063 g/mL. Radioactivity in the total plasma, in the heparin–MnCl2 supernatant (containing the HDL), and in the ultracentrifugal fractions of d<1.063 g/mL and d>1.063 g/mL was measured in a Beckman LS 6000TA scintillation counter. In the samples separated by precipitation, the difference between total plasma and HDL counts was taken as the counts in the VLDL/LDL fraction. Lipids in the total plasma and in the isolated HDL and VLDL/LDL fractions were extracted according to the method of Folch. The lipid extract was subjected to thin layer chromatography (TLC), using hexane-diethyl ether-methanol-acetic acid, 90:20:3:2 (v/v/v/v), to separate FC from CE. Having established that there were no measurable counts in FC in any sample, the total counts before TLC were taken as the CE counts.

**Assay of CETP Activity**

Activity of CETP was assessed as the transfer of [3H]-labeled CE from rHDL to LDL as described.22 The labeled HDL (final total cholesterol concentration 80 nmol/mL), LDL (final total cholesterol concentration 240 nmol/mL), and 50 μL of rabbit plasma (or the plasma of rabbits that were either untreated or had received the oral CETP inhibitor for 5 days) were added to 1.25 g/mL of pooled, human plasma as a positive control) in a final incubation volume of 175 μL. After incubation at 37°C for 3 hours in the presence of 10 μL of 14.2 mg/mL DTNB (to inhibit LCAT activity). At the end of incubation, LDL was precipitated by heparin and MnCl2 and the supernatant was recovered and assayed for radioactivity. The loss of label from HDL was linear so long as...
<30% of [3H]CE had been transferred. CETP activity is expressed as nmol CE transferred/mL plasma/hour.

Other Analyses

Chemical assays were performed in an automated chemical analyzer (Boehringer Mannheim Diagnostics/Hitachi) using commercial kits to measure the total cholesterol (TC), FC, and phospholipid concentrations (Boehringer-Mannheim, GmbH). CE concentrations were calculated as the difference between TC and FC concentrations. The concentration of apoA-I was measured immunoturbidometrically using sheep anti-rabbit apoA-I antibodies.

Compartmental Modeling

Data were analyzed using multi-compartmental analysis (SAAM II) and fitted to the 2-compartmental model shown in Figure 1. Two assumptions were made: (1) given that the concentration of VLDL CE was very low, the VLDL/LDL fraction has been treated as a single pool; and (2) that the sole entry of CE into the system is via the HDL pool (Figure 2a). In the absence of any previously reported studies of HDL kinetics, the coefficient of variation associated with the fractional catabolic rate (FCR) is ~15%. Thus, with an FCR of 0.0068 per minute (the average HDL CE FCR of the control rabbits in study 1), the SD is 0.001. If we assume a power of 80% with a 2-tail 5% level of significance and we expect a minimal effect on FCR of 30% (difference in means of 0.002), then we require 5 animals per group. With 13 per group (6 + 7), the power of the study is >99%. It should be noted, however, that the study was not powered to test for effects on HDL CE production, because there is, a priori, no evidence to suggest that HDL production is altered by CETP inhibition. Thus, the study has been powered solely according to expected changes in HDL CE catabolism (FCR). However, because the HDL CE flux is the product of the FCR and the measured pool size, the study is clearly also adequately powered to detect differences in the rates of HDL CE production and removal.

Comparisons of treatment groups were performed using Student t test and 1-way ANOVA with JMP software (SAS Institute).

Results

Characterization of Labeled HDL

Spherical rHDL Containing [3H]CE

The spherical rHDL had a Stokes diameter of 8.8 nm and a molar ratio of PLPC/CE/apoA-I of 40:12:1.

Native HDL Containing [3H]CE

The native HDL isolated from the control donor rabbits had a Stokes diameter of 11.0 nm and a percent mass composition of 33%, 16%, 11%, 5%, and 35% for phospholipids, CE, triglyceride, FC, and apoA-I, respectively. The native HDL isolated from CETP inhibitor-treated donor rabbits had a Stokes diameter of 11.4 nm and a percent mass composition of 31%, 22%, 4%, 5%, and 38% for phospholipids, CE, triglyceride, FC, and apoA-I, respectively. Analysis using TLC confirmed that >95% of the total label resided in the CE moiety.

Lipid Concentrations and CETP Activity

Studies using labeled rHDL as tracer are identified in the Table and in the text as study 1 and those using labeled native HDL are identified as study 2. Administration of the CETP inhibitor reduced the plasma CETP activity in the treated animals from 33.4 to 3.5 nmol CE transferred/mL plasma/hour in study 1 and from 24.6 to 3.1 nmol CE transferred/mL plasma/hour in study 2. The inhibitor had no measurable effect on the plasma activity of PLTP. The concentration of HDL CE was 0.46 and 0.86 mmol/L (P<0.05) in the untreated and treated rabbits, respectively, in study 1, and 0.33 and 0.64 mmol/L (P<0.05) in the untreated and treated rabbits, respectively, in study 2. The VLDL/LDL CE concentrations were 0.28 and 0.11 mmol/L (P<0.05) in the untreated and treated rabbits, respectively, in study 1, and 0.22 and 0.22 mmol/L (not significant), in the untreated and treated rabbits, respectively, in study 2 (Table). In study 1, CETP inhibition was accompanied by an increase in the plasma concentration of apoA-I from 0.41 to 0.66 mg/mL (P<0.05).

HDL CE Kinetics

Studies Using Labeled rHDL (Study 1)

In the untreated animals, there was a progressive clearance of the injected [3H] CE from the HDL pool (Figure 2a). In the
animals treated with the CETP inhibitor, the loss of label from the HDL pool was slower (240 minutes versus 90 minutes for the loss of 50% of the label). In the untreated animals, a proportion of the injected [3H] CE appeared in the VLDL/LDL fraction, reaching a peak at 60 minutes after the injection. This contrasted with the situation in the animals treated with the inhibitor. In these animals, there was minimal appearance of labeled CE in the VLDL/LDL fraction compared with that in the untreated animals.

The 2-pool model shown in Figure 1 was fitted to the tracer data. The fit of the model to the CE radioactivity curves for HDL and VLDL/LDL is shown in Figure 2a. The best fit of the model to the observed data in the control animals indicated that approximately half of the removal of HDL CE from plasma was via the direct pathway and half by the indirect pathway via VLDL/LDL (Table). The total removal of HDL CE from the plasma by the sum of both pathways was 3.1 μmol/L/min. Confidence in this value was increased by finding that the calculated total removal from plasma was unchanged by constraining the model so as to permit removal exclusively by the direct pathway (3.2 μmol/L/min) or exclusively by the indirect pathway (3.1 μmol/L/min).

When the results from the animals treated with the CETP inhibitor were modeled, the calculated values for fluxes between HDL and VLDL/LDL were too low to be estimated with confidence and have been taken as zero. This is consistent with the observed VLDL/LDL tracer data showing minimal CE transfer from HDL particles. As a consequence, the model-derived removal of HDL CE by the indirect pathway via VLDL/LDL, FLUX (0,2), was consistently zero in the treated animals, with 100% being removed from plasma directly via the HDL fraction. The value of FLUX (0,1) in these treated animals was 2.72 μmol/L per minute, a value that was not significantly different from the total flux.

Figure 2. In vivo metabolism of [3H]cholesteryl esters ([3H]CE) in rabbits after intravenous injection of HDL containing [3H]CE. Decay curves of [3H]CE in HDL and its appearance in the VLDL/LDL fraction are shown in the presence and absence of CETP inhibition (CETPi). A, Results of study 1 using [3H]CE in spherical rHDL as a tracer. Each point and bar represents the mean and SD of 6 animals in both the untreated and CETPi-treated groups. B, Results of study 2 using [3H]CE in native HDL as a tracer. Each point and bar represents the mean and SD of 6 animals in the untreated group and 7 animals in the CETPi-treated group.
(direct plus indirect pathways) in the untreated animals (Figure 3a). Thus, in rabbits treated with the CETP inhibitor, there was no evidence that blocking of the removal of HDL CE by the indirect pathway via VLDL/LDL compromised the total removal of HDL CE from plasma.

Studies Using Labeled Native HDL (Study 2)

To validate the results obtained using labeled rHDL as a tracer, another set of kinetic studies was conducted using labeled native HDL as the tracer. As in the previous study, CETP inhibition increased the concentration of HDL CE but had no effect on the concentration of CE in the VLDL/LDL fraction. Preparations of native HDL isolated from 2 control and 2 CETP-inhibited donor animals were radio-labeled in the CE moiety. Each preparation of labeled control HDL was injected into 3 control recipients (to give a total of n=6) and each preparation of labeled HDL from a CETP inhibited animal was injected into 3 (or 4) CETP inhibited recipients (to give a total of n=7) (Figure 2b). When native HDL was used as a tracer, the mass of [3H] CE from the HDL pool was again slower in the CETP inhibitor treated animals than that observed in untreated rabbits (300 minutes versus 120 minutes, respectively, for loss of 50% of the label).

As in the studies using rHDL as the tracer, there was an observable transfer of CE from HDL to the VLDL/LDL fraction in the control animals that was largely abolished in the CETP-inhibited animals. The calculated total HDL CE flux (direct plus indirect pathways) (Table) was lower in both groups of animals in study 2 than in those in study 1 in which labeled rHDL was used as a tracer. There was also a smaller proportion of the HDL CE removed by the direct pathway in the untreated animals in study 2 compared with study 1. These differences may have been due to differences in the form in which the tracer was injected but may also have reflected the lower concentration of CE in the animals in study 2. However, as in study 1, the total HDL CE flux in study 2 was not significantly different between the untreated (1.84 μmol/L/min) and CETP-inhibited (1.61 μmol/L/min) animals (Figure 3b), again indicating that CETP inhibition does not compromise the overall removal of HDL CE from plasma.

Discussion

CETP inhibition as a potential anti-atherosclerotic therapy has been somewhat controversial. Despite the fact that CETP inhibition increases HDL cholesterol levels in rabbits and humans, it has been suggested that this may be at the expense of a reduction in the pathway of reverse cholesterol transport. The final step of this pathway involves the delivery of HDL CE to the liver. This step can occur by either of 2 distinct processes: a direct pathway mediated by SR-BI and an indirect pathway dependent on the CETP-mediated transfer of HDL CE to VLDL/LDL lipoproteins. It is possible that the direct pathway may become rate-limiting when the indirect pathway is blocked by CETP inhibition, leading to a reduction in total plasma HDL CE removal.

The current study is the first to describe how CETP inhibition impacts on the kinetics of plasma HDL CE transport in vivo. Rabbits were the species of choice for these studies because, like humans, they possess a high level of activity of CETP in plasma. As a consequence, a proportion of their HDL CE is removed from plasma via the indirect CETP-mediated pathway. Administration of the CETP inhibitor CP-456,643 to the rabbits in the current study inhibited CETP activity by an 80% to 90% and almost completely blocked the transfer of CE from HDL to the VLDL/LDL fraction. This led not only to an increase in the concentration of HDL CE but also to a virtually complete suppression of the indirect pathway of HDL CE removal. However, these effects were not accompanied by a reduction in the total flux of HDL CE, indicating that neither the rate of production nor the overall removal of HDL CE from plasma was compromised. This result was independent of whether the CE tracer was contained in spherical rHDL (comparable to those we have used and validated previously to investigate the kinetics of HDL apoA-1) or as a component of native HDL. The fact that the nature of the tracer had little impact on the results adds greatly to the confidence in the conclusions drawn from these studies.

These findings are in agreement with a previous report in humans in which CETP inhibition had little impact on overall reverse cholesterol transport as assessed by neutral sterol excretion in feces. Our results are also consistent with those in studies of transgenic mice expressing varying amounts of simian CETP in which it was found that the delivery of cholesterol from extra-hepatic tissues to the liver was constant despite a 4-fold variation in concentration of HDL cholesterol levels. It was concluded that, at least in the mouse, neither the concentration of HDL nor the level of...
CETP activity had an impact on the delivery of cholesterol from extrahepatic organs to the liver.

Additional circumstantial evidence that CETP may be of only minor importance in promoting the delivery of HDL cholesterol to the liver has been obtained from kinetic modeling studies of human plasma cholesterol transport. The authors of this study concluded that a significant proportion of HDL cholesterol is delivered from the plasma to the liver in the form of FC.28 Because CETP does not affect HDL–FC transport, variations in CETP, either its expression in mice29 or its inhibition in humans,25 would have no effect on the FC component of directly measured reverse cholesterol transport.

The possibility has been raised that inhibiting CETP may be detrimental by virtue of generating very large HDL particles that may be ineffective as acceptors of cell cholesterol in the process mediated by ABCA1, for which poorly lipidated apoA-I is the preferred acceptor.30 However, there are pathways other than ABCA1 that promote the removal of cholesterol from cells.31 For example, the efflux of cholesterol from macrophages is also mediated by SR-BI2,32,33 and by the recently described ABCG1 transporter.34,35 Unlike the efflux that is promoted by ABCA1, the preferred acceptors for these other pathways are larger, spherical HDL.36 Thus, it may be argued that the increased concentration of the larger HDL particles associated with low activity of CETP activity37 may enhance rather than inhibit the efflux of cholesterol from macrophages.

It should be noted that a release of cholesterol from macrophages in the artery wall is miniscule compared with that released from all other tissues in the body. As a consequence, even a major increase in the efflux of cholesterol from macrophages in the artery wall after CETP inhibition would have minimal impact on overall reverse cholesterol transport, whether measured in terms of HDL CE transport in plasma as in the present study or the excretion of neutral sterols in feces.29 But even if the efflux of cholesterol from macrophages were unchanged, the substantial increase in HDL concentration associated with CETP inhibition has the capacity to be anti-atherogenic by virtue of increasing the anti-inflammatory,48–50 anti-oxidant,41,42 and anti-thrombotic43,44 activities attributed to this lipoprotein fraction.

Several species, including rats, mice, and dogs are naturally deficient in CETP.45 In these species, plasma CE is transferred to other lipoprotein fractions in these species, the removal of HDL CE from the plasma can occur only via the direct pathway. It is interesting to note that these species also tend to be resistant to the development of atherosclerosis. Moreover, the introduction of the CETP gene into mice has been reported to be pro-atherogenic.4 However, that there are also experimental conditions under which the expression of CETP in mice is anti- rather than pro-atherogenic.5,7

The effects of CETP inhibition on atherosclerosis in rabbits have been generally more consistent. Like humans, rabbits express levels of CETP and, also like humans but unlike mice, are highly susceptible to the development of atherosclerosis. With one exception,8 the inhibition of CETP in rabbits, whether by the use of antisense oligodeoxynucleo-
tides directed against CETP,2 an anti-CETP vaccine,3 or a small molecule inhibitor of CETP,4 is associated with a significant reduction in the progression of atherosclerosis.

In conclusion, with the obvious reservation that these studies have been conducted in rabbits and should be extrapolated to humans with caution, these experimental results provide a measure of reassurance that inhibition of CETP does not compromise the removal of HDL CE from plasma and is therefore unlikely to be pro-atherogenic in humans. We must now await the results of intervention trials designed to directly test the hypothesis that inhibition of CETP will be anti-atherogenic in humans.

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[References are provided in the original document but are not transcribed here.]
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