We have determined the role of cholesteryl ester transfer protein (CETP) in selective uptake of high density lipoprotein (HDL)-derived cholesteryl esters (CE) by human adipose tissue, using organ culture or collagenase-digested adipocytes. Incubation of the fresh tissue fragments with HDL containing \(^{3}H\)CE or \(^{125}\)I-apo-protein (apo) A-I resulted in significant uptake of HDL-CE-derived label. Addition of recombinant CETP (rCETP) increased CE uptake in a dose-response fashion. In contrast, little association of \(^{125}\)I-apo-A-I with adipose tissue was noted, and addition of rCETP did not alter apoA-I uptake or degradation. Incubation of adipose tissue with TP2, an anti-CETP monoclonal antibody, which inhibits neutral lipid transfer, markedly reduced selective uptake of HDL-CE. Studies using human adipocytes isolated by collagenase digestion also demonstrated selective uptake of HDL-CE and enhancement of this process by rCETP. To confirm that the association of HDL-CE-derived radioactivity with adipose tissue was not due to neutral lipid exchange between adipocytes and HDL, we measured changes in HDL composition following incubation of HDL and rCETP with isolated adipocytes. A decrease in HDL-CE concentration in the medium was observed, an effect which was markedly attenuated when incubations were carried out in the presence of monoclonal antibody TP2.

Furthermore, the decrease in HDL-CE was accompanied by an increase in HDL free cholesterol, likely representing efflux of adipocyte cholesterol to HDL. There were no significant changes in phospholipid, apoA-I, or apoA-II in the medium following incubation with adipocytes. These data demonstrate a novel and important role for CETP in selective uptake of HDL-cholesteryl esters by human adipocytes and suggest that this pathway may be of physiological significance in HDL remodeling and adipocyte cholesterol accumulation.

Uptake of HDL\(^{3}\)-derived CE by adipocytes has been well documented and, in the obese state, plasma HDL-CE may be reduced as a consequence (1–3). The uptake of CE by adipose tissue is disproportionately greater than the uptake of HDL apolipoprotein (1, 4, 5). Thus, CE are transferred from HDL to adipocytes by a nonendocytic process, known as selective cholesterol uptake (6–9). The selective uptake of CE by adipose cells resembles in many ways the processes described in vivo for rat liver, ovary, and adrenal (6) and in vitro for adrenal cells (7, 10) and rat luteal cells (11). While many similarities in selective cholesteryl ester uptake have been noted in several tissues, the physiological consequences vary with cellular processing. It is likely that HDL can deliver cholesterol in the esterified form to adipocytes, where it is hydrolyzed to free cholesterol, which can then be stored in the oil droplet, equilibrate with the membrane, or efflux from the cell over time (12, 13).

The role of CETP in reverse cholesterol transport has been well characterized (14). CETP is highly expressed in mammalian adipose tissue (15). There is also evidence of CETP activity associated with adipocyte plasma membranes (16). We have demonstrated that immunoreactive CETP is present on the adipocyte plasma membrane and that CETP gene expression is greatest in very small fat cells (10–50 \(\mu\)m), which are likely to be in a trophic phase and thus to have a particular requirement for lipoprotein cholesterol (17). This led us to test the hypothesis that human adipocyte CETP functions to facilitate uptake of HDL cholesteryl esters. Our findings demonstrate a novel function for CETP in human adipocyte cholesterol metabolism.

**EXPERIMENTAL PROCEDURES**

**HDL Isolation and Labeling**—Plasma was collected from healthy normolipemic donors. HDL (\(d = 1.063–1.21\ \text{g/ml}\)) were isolated by sequential ultracentrifugation (Beckman 55.2 Ti rotor, 40,000 rpm, 20 h, 8 °C).

**Lipoprotein Labeling with \(^{3}H\)Cholesteryl Oleate (31)**—Approximately 200 \(\mu\)Ci of \(^{3}H\)cholesterol oleate were added to 15 mg of palmitoyl oleyl phosphatidylcholine dissolved in chloroform and evaporated under \(N_{2}\). Three ml of PBS were added, and the mixture was sonicated to create palmitoyl oleyl phosphatidylcholine-\(^{3}H\)cholesterol oleate vesicles. The vesicles were added to the entire quantity of isolated HDL and incubated at 37 °C, overnight, with agitation to permit transfer of labeled cholesteryl oleate to HDL. Vesicles were separated from the labeled lipoproteins by ultracentrifugation (Beckman 100.4Ti rotor, 60,000 rpm, 15 h, 8 °C) and HDL (\(d = 1.063–1.21\)) were isolated by two successive ultracentrifugations (Beckman 100.4Ti rotor, 57,000 rpm, 25 h, 8 °C).

**Lipoprotein Labeling with \(^{125}\)I—Purified human apoA-I was iodinated using \(^{125}\)I-IODO-BEADS (32). The beads were equilibrated in phosphate buffer (0.3 m NaPO\(_4\), pH 7.4) and then incubated with 20 \(\mu\)l of \(^{125}\)I (2 mCi of NaI) in 70 \(\mu\)l of phosphate buffer for 5 min at room temperature. 150 \(\mu\)g of apoA-I were added to the mixture and incubated chromatography; PL, phospholipid; FC, free cholesterol.
at room temperature for 45 min with agitation. Unincorporated label was removed by passing the mixture through a desalting column (Ex- cellulose GF5, Pierce) which had been preswashed in 0.1% bovine serum albumin in PBS followed by PBS. Labeled apoA-1 was equilibrated with 35 mg of HDL (previously isolated) at 37 °C for 4 h with gentle agitation. The homogenate was then centrifuged (Beckman 100.4 Ti rotor, 40,000 rpm, 40 h, 8 °C).

Lipoprotein Labeling with [3H] and [125I]—To obtain doubly labeled HDL with 3H in esterified cholesterol and 125I in apoA-I, the [3H]HDL was then equilibrated with labeled apoA-1 as described above.

The HDL-containing fraction was dialyzed against PBS overnight and deoxycholate with respect to initial specific activity. Results were expressed as nanograms of HDL protein/mg of total core lipid. Each data point represent the mean ± S.E. for three samples. Results are representative of three experiments.

activity using a gamma counter. In another experiment, the infranatant was ultracentrifuged to separate the membrane fractions (pellet) from the cytosolic fraction (supernatant). Proteins from these fractions were precipitated by trichloroacetic acid methods (25) and 125I-associated radioactivity was counted. ApoA-I was quantitated with respect to initial specific activity. Results are expressed as nanograms of HDL protein/mg of total core lipid determined as described above.

HDL-ApoA-I and ApoA-II Composition—ApoA-I and ApoA-II were quantified by immunoelectrodiffusion in agarose gel using the Hydrafuge A/B and A-II kit (Sebia, France).

Statistics and Calculations—Data are expressed as mean ± S.E. Significant of differences was examined using Student’s t test for unpaired data. Cellular uptake of HDL tracers is shown as apparent HDL particle uptake, as indicated by the cell content of each tracer (6). This apparent uptake is expressed in terms of HDL protein, to compare uptake of both tracers on the same basis.

RESULTS

The time course pattern of uptake of HDL by human adipose tissue is illustrated in Fig. 1. The uptake of cholesteryl ester from HDL was most rapid over the 1st h but continued to increase over 4 h (Fig. 1), suggesting that the adipocyte membrane capacity as a cholesteryl ester acceptor is not limiting. This experiment was repeated with HDL labeled with 125I-apoA-I to determine if the tissue-associated radioactivity was due to selective uptake of HDL-derived CE or to particle uptake. In contrast to the pattern of a continuous increase in [3H]CE uptake with time, little 125I-ApoA-I became associated with adipose tissue within 30 min of incubation and the level of cell-associated 125I-apoA-I declined by 2 h and remained constant thereafter (Fig. 1). These experiments confirm the phenomenon of selective uptake of HDL-derived CE by human adipose tissue, in accord with previous reports (1, 4, 5).

Human adipocytes synthesize and secrete CETP (15). To determine whether the observed selective uptake of HDL-CE could be further enhanced by exogenous CETP, 4-h incubations were performed following addition to the medium of physiological plasma concentrations (0.6, 1.2, 2.4 μg/ml) (19) of recombinant human CETP (rCETP). CETP was shown to have a linear dose-response enhancing effect on the selective uptake of cholesteryl ester from HDL. In the absence of exogenous rCETP, there was a smaller but nonetheless significant uptake of HDL-derived cholesteryl ester by adipose tissue demonstrating that this is a physiological process, which is likely to be mediated, in part, by adipocyte CETP. In contrast to its effects
on CE, increasing amounts of rCETP did not increase cell-associated 
125I-apoA-I, demonstrating that the observed uptake of [3H]CE by adipose tissue was not due to particle uptake 
(Fig. 2).

The effect of exogenous rCETP (2.4 µg/ml of medium) on the time course pattern of selective uptake is shown in Fig. 3. Using adipose tissue fragments obtained from another normal subject, we found that in the presence of rCETP, selective CE uptake was more rapid and continuous and did not plateau at 4 h. These data confirm that adipocyte membrane capacity as a cholesteryl ester acceptor is not limiting in presence of rCETP. Results of experiments using adipose tissue fragment from different patients (Figs. 1–3) demonstrate individual variation in the extent of selective uptake of HDL-CE possibly due to differences in adipocyte size and adipose tissue matrix composition.

Monoclonal antibodies (mAbs) against different epitopes of the CETP molecule (26, 27) were used to verify that the observed HDL-CE uptake was mediated by CETP. To eliminate steric hindrance artifact, we prepared Fab fragments for these studies. The anti-CETP mAb, TP2, which reacts with an epitope in the carboxyl end of the molecule and which inhibits neutral lipid transfer (27), had no effect on cell-associated 125I-apoA-I after a 4 h incubation (data not shown). However, TP2 reduced selective uptake of HDL-CE by human adipose tissue by 70 ± 3.5% (p = 0.03). When studies were carried out in the presence of CETP, TP2 reduced selective uptake by 54 ± 1.4% (p = 0.05) (Fig. 4) showing that the neutral lipid transfer activity of CETP is essential to this process. The observed CETP-mediated uptake was not due to CETP associated with labeled HDL since removal of trace amounts of CETP from HDL by TP2 immunoaffinity did not affect selective uptake (data not shown). It is thus likely that CETP endogenously synthesized by adipocytes mediates selective uptake of HDL-CE by adipose tissue, accounting for the TP2-inhibitable selective uptake of HDL-CE. Although the neutralizing mAb, TP2, reduced selective uptake, this effect was not enhanced when the concentration of TP2 was doubled, indicating that the levels added were sufficient to block most, but not all, HDL-CE uptake. Thus, additional mechanisms, not involving CETP, may account for a portion of the selective uptake of HDL-derived CE by human adipose tissue.

Adipose tissue contains adipocytes and other cell types including endothelial cells, fibroblasts and macrophages. To ascertain that these other adipocyte tissue constituents were not responsible for selective uptake, we studied the uptake of HDL-CE and its stimulation in presence of rCETP using isolated human adipocytes. When studies were carried out with singly ([3H]CE) or doubly labeled ([3H]CE and 125I-apoA-I) HDL, results were similar to experiments performed with adipose tissue fragments, indicating an increase in CE uptake over time and association of 125I-apoA-I with adipocytes after 1-h incubation followed by a slow decline in cell associated apoA-I counts over 18 h (Fig. 5). These data were confirmed by quantification of apoA-I protein associated with adipocyte cytosol and membrane. Our results indicate that when HDL is incubated with adipocytes or adipose tissue, a small amount of apoA-I associates with the adipocyte membrane before being released or degraded. Trichloroacetic acid precipitation of 125I-apoA-I derived counts revealed that only 20 ± 5% of the small fraction of apoA-I which became associated with adipocytes...
CETP Mediates HDL-CE Uptake

FIG. 5. Time course of HDL binding and cholesteryl ester uptake by primary human adipocytes. Isolated adipocytes were incubated in culture medium containing HDL (50 μg/ml) singly labeled with [3H]cholesteryl oleate or doubly labeled with [3H]cholesteryl oleate and 125I-apo-A-I. At indicated times (1–18 h), adipocytes were washed and homogenized, and lipids were extracted to measure 3H radioactivity from singly labeled HDL (A). In another experiment, at the end of incubations periods, adipocytes doubly labeled with [3H]cholesteryl oleate and 125I-apo-A-I were washed and homogenized in homogenization buffer. The infranatant (membrane and cytosol) was ultracentrifuged to separate the membrane fraction (pellet) (C) from the cytosolic fraction (supernatant) (D). Proteins from these fractions were trichloroacetic acid-precipitated and 125I-apo-A-I derived counts measured. Results are expressed as nanograms of HDL protein/mg of total core lipid. Each data point represents the mean ± S.E. for three samples.

was taken up and degraded.

To verify that the apoA-I labeling protocol did not alter the HDL composition, this experiment was performed with doubly labeled HDL with 125I-apo-A-I and [3H]CE. Comparison of singly and doubly labeled HDL revealed that there was no effect of the labeling procedure on the HDL particle composition (PL, FC, CE, apo-A-I, and apo-A-II). Nor was there an effect of the labeling procedure on the time-course pattern of HDL-CE uptake (data not shown). For studies with doubly labeled HDL particles, we measured only cell associated, 125I-apo-A-I derived radioactivity since γ counts could be determined without interference of β counts (Fig. 5).

The phenomenon of selective uptake of HDL-CE was clearly demonstrable in studies with isolated adipocytes (Fig. 6). Compared with above data (Figs. 2 and 3), albeit from different subjects, it appears that the effect of rCETP on selective uptake of HDL-CE may be greater in isolated adipocytes than in adipose tissue fragments (10-fold versus 2–5-fold increase in CE uptake, respectively). The removal of the adipose tissue matrix in primary adipocyte cultures may explain the enhanced effect of rCETP on selective uptake of HDL-CE.

We also measured changes in HDL lipid and protein composition and adipocyte membrane cholesterol before and after incubation with the cells. After 4 h of incubation of HDL with primary adipocytes, the CE content of HDL decreased by 37% (p < 0.01). In contrast, the free cholesterol mass increased 9-fold (p = 0.0001), whereas the PL content (Fig. 7) and ratio of apo-A-I/apo-A-II (data not shown) were not affected. No change in HDL-TG content was detectable by enzymatic assay (data not shown). When HDL was incubated with adipose tissue in the absence of added rCETP, adipocyte plasma membrane cholesterol decreased by 30% after 4 h of incubation (Fig. 9), likely representing efflux, to HDL, of adipocyte membrane cholesterol (endogenous membrane cholesterol as well as free cholesterol derived from CE acquired from HDL). In the presence of rCETP (2.4 μg/ml), the cholesterol content of the membrane was restored to baseline (Fig. 8). This likely reflects the balance of increased CE uptake mediated by rCETP, CE hydrolysis, transfer of FC to both membrane and core lipid compartments and continued cholesterol efflux to HDL (Fig. 8). Addition of rCETP (2.4 μg/ml) to the medium containing HDL incubated with adipocytes did not alter the FC and PL composition of HDL but induced a further and significant 23% decrease in HDL-CE compared with a control without addition of rCETP (p = 0.023) (Fig. 7). This effect was markedly attenuated when incubations were carried out in the presence of the neutralizing mAb, TP2 (data not shown).

FIG. 6. Effect of rCETP on cholesteryl ester uptake by isolated human adipocytes. Isolated adipocytes were incubated for 4 h in culture medium containing HDL (50 μg/ml) labeled with [3H]cholesteryl oleate in presence or absence of rCETP (2.4 μg/ml). At the end of incubation, adipocytes were homogenized and lipid-associated 3H radioactivity was measured. Results are expressed as nanograms of HDL protein/mg of total core lipid. Each data point represents the mean ± S.E. for three samples. Results are representative of three similar experiments. a, p < 0.05.

FIG. 7. Effect of rCETP on HDL composition. Isolated adipocytes were incubated for 4 h in culture medium containing HDL (50 μg/ml) labeled with [3H]cholesteryl oleate in the presence or absence of rCETP. At the end of the incubation, HDL were removed from medium, and lipid composition was determined. Lipids were extracted and FC, CE, concentration were determined by gas liquid chromatography and HPTLC and PL by HPTLC. Base-line HDL composition is shown as ■, in comparison to HDL composition following incubation in presence (●) or absence (□) of rCETP. Each data point represent the mean ± S.E. for three samples. Results are representative of three similar experiments. a, p < 0.05; b, p < 0.005.

DISCUSSION

Adipose tissue is composed of adipocytes and adipocyte precursors interspersed in an abundant capillary layer, held together by connective tissue. Freshly isolated human fat cells studied ex vivo maintain the properties of in vivo cells (3, 28) in terms of HDL binding and cholesterol uptake. Adipocytes have very limited capacity for cholesterol synthesis and are highly dependent on lipoproteins as a source of cholesterol to maintain a relatively fixed ratio of cholesterol to triglyceride in the core lipid droplet. We have defined a novel role for CETP in medi-
cerebroside can be prevented by addition of rCETP to the media (Fig. 8). In other studies, we have reported that CETP mRNA abundance is significantly correlated with membrane cholesterol (17), suggesting that there is a pool of membrane cholesterol which regulates CETP gene expression. The requirement for exogenous lipoprotein derived cholesterol would be expected to be greatest for immature lipid poor adipocytes and, consistent with this hypothesis, we have shown that CETP mRNA abundance is greater in very small fat cells (10–50 μm in diameter) in comparison to mature adipocytes (50–200 μm) (17).

In the present experiments, following incubation of HDL with adipose tissue, we noted a significant decrease in HDL-CE (Fig. 7), consistent with the observed uptake of [3H]CE-derived counts by adipose tissue. In addition, the ratio of FC to PL increased in HDL and decreased in the adipocyte membrane suggesting net movement of free cholesterol to HDL in accord with previous studies showing net efflux of adipocyte free cholesterol to HDL receptor particles (36). The transfer of free cholesterol between cells and HDL particles is likely to be bidirectional, involving diffusion of cholesterol in the aqueous space between the plasma membrane and the lipoprotein surface (37–40). When these incubations were carried out in the presence of rCETP, HDL was further depleted of CE, and adipocyte membrane cholesterol was restored to baseline. These changes in HDL and adipocyte membrane lipid composition are likely to reflect the balance of CE uptake which is facilitated by CETP, CE hydolysis, transfer of free cholesterol to the core lipid droplet and plasma membrane, and efflux of free cholesterol to HDL. Following incubation of HDL with adipose tissue either in the presence or absence of rCETP, no change in the ratio of apoA-I to apoA-II in HDL or in the concentration of adipocyte membrane-associated apoA-I was noted.

Preferential cholesteryl ester uptake by adipocytes and steroidogenic cells implies that HDL can deliver cholesterol without undergoing catabolic degradation through a lysosomal process. It is likely that there are several independent regulatory mechanisms at various stages between the delivery of HDL-CE to the adipocyte plasma membrane and subsequent uptake and intracellular metabolism. Little is known regarding cholesterol exchange between core and membrane cholesterol. Despite a disproportionate uptake of HDL core lipid, the process may not be completely independent of HDL-apolipoprotein interaction and cholesteryl ester transfer to the adipocyte may involve a specific apolipoprotein. In previous studies, using isolated human adipocytes, a correlation between HDL binding and cholesteryl ester uptake was demonstrated (4). The non-endocytotic mechanism for selective uptake may be mediated by an interaction with a cell surface lipoprotein binding domain. Cultured adipocytes actively synthesize and secrete apoE and lipoprotein lipase (41) as well as heparin sulfate proteoglycans (HSPG) which bind lipoprotein lipase and apoE (42). Adipocytes express various receptors involved in lipoprotein catabolism, including the LDL-receptor (43), LDL-related receptor protein (44), and very low density lipoprotein-receptor (45). Little is known about the interaction between these molecules and the adipocyte membrane. The fact that the effect of rCETP on selective uptake is greater when HDL is incubated with isolated adipocytes as compared with adipose tissue fragments suggests that the collagenous matrix of adipose tissue may have impeded the effect of exogenous rCETP on selective uptake. Other components of the matrix surrounding adipocytes may, however, mediate lipoprotein interactions. In other experiments (data not shown) disruption of the adipose tissue HSPG matrix with heparinases, reduced selective uptake of

![Graph](http://www.jbc.org/)

**Fig. 8.** Changes in membrane lipid composition following incubation with HDL. Isolated adipocytes (same patient illustrated in Fig. 7) were incubated for 4 h in culture medium containing HDL (50 μg/ml) labeled with [3H]cholesteryl oleate in presence or absence of rCETP. Adipocytes labeled with [3H]cholesteryl oleate were homogenized. The infranatant (membrane and cytosol) was ultracentrifuged to separate the membrane fraction (pellet) from the cytosolic fraction. Lipids were extracted as described and mass was determined by gas liquid chromatography for FC and HPTLC for PL. Base-line adipocyte membrane composition is indicated as □ and composition following incubation with HDL in the presence of rCETP as ■ and in the absence of rCETP as □. Results obtained from three experiments are shown and are expressed as percent of control. a, p < 0.05.
HDL-CE, suggesting that HSPG may facilitate the interaction of HDL with the adipocyte plasma membrane. Further studies are under way to determine whether CETP-mediated uptake of HDL-derived CE by adipocytes is dependent upon interaction of apoA-I or apoE with the adipocyte membrane or HSPG complex.

These data demonstrate that CETP plays a novel and important role in the selective uptake of CE from HDL by human adipocytes and suggest that this pathway may be of quantitative physiological significance in HDL remodeling and adipocyte cholesterol accumulation. Obesity is commonly associated with hypertriglyceridemia and it is possible that CETP-mediated clearance of HDL-CE by adipose tissue may contribute to this phenotype.

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