Apolipoprotein A-I Induces Translocation of Cholesterol, Phospholipid, and Caveolin-1 to Cytosol in Rat Astrocytes*

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Intercellular cholesterol transport in the brain is carried by high density lipoprotein (HDL) generated in situ by cellular interaction with the apolipoprotein apoE, which is mainly synthesized by astrocytes, and with apoA-I secreted by cells such as endothelial cells. Rat astrocytes in fact generate HDL with extracellular apoA-I in addition to releasing HDL with endogenously synthesized apoE, seemingly by the same mechanism as the HDL assembly for systemic circulation. Relating to this reaction, apoA-I induced translocation of newly synthesized cholesterol and phospholipid to the cytosol prior to extracellular assembly of HDL, accompanied by an increase of caveolin-1 in the cytosol, activation of sterol regulatory element-binding protein, and enhancement of cholesterol synthesis. The lipid translocated into the cytosol was recovered in the fraction with a density of 1.09–1.16 g/ml as well as caveolin-1 and cyclophilin A. Cyclosporin A inhibited these apoA-I-mediated reactions and suppressed apoA-I-mediated cholesterol release. The findings suggest that such translocation of cholesterol and phospholipid into the cytosol is related to the apo A-I-mediated HDL assembly in astrocytes through functional association with caveolin-1 and a cyclophilin A-sensitive cyclophilin protein(s).

The central nervous system (CNS) is sheltered from interaction with the lipoproteins of the systemic circulation by the blood-brain barrier. Therefore, extracellular cholesterol transport in the CNS is mediated by its own lipoprotein system, consisting mainly of the particles equivalent to plasma HDL. The main apolipoproteins are apoE produced by astrocytes (2), microglia (3), and apoA-I from an unknown source but reportedly secreted by brain endothelial cells (4). The astrocytes were shown to generate HDL, not only with endogenously synthesized apoE but also with exogenous apoE and apoA-I (5).

The apolipoprotein-cell interaction that generates HDL is common for many somatic cells from various origins and is distinct from the diffusion-mediated cholesterol efflux from the cell surface (6). The reaction is a main source of plasma lipoprotein (7) and is also one of the major pathways for cholesterol release from the cells (8). Generation of HDL with cellular phospholipid seems to require a cellular interaction site with apolipoprotein. An intracellular cholesterol trafficking system linked to such interaction is responsible for incorporation of cholesterol into the HDL (9, 10). Mutations in the ABCA1 transporter protein were identified in patients with plasma HDL deficiency who lack the ability to generate HDL by this reaction (11–13). Thus, the reaction depends on the cellular system to export materials. A specific intracellular cholesterol transport system is important to make the HDL cholesterol-rich. In macrophages and smooth muscle cells, protein kinase C was shown to be involved in this trafficking (9, 10).

It is not known whether the mechanism for generation of HDL in somatic cells is different from that for the HDL assembly in the CNS. There are, however, a few unique findings concerning HDL generation by CNS cells. We have reported in a previous study (5) that the cultured rat astrocytes produce cholesterol-poor and phosphatidylcholine-rich HDL with exogenous apoA-I, whereas the HDL formed with endogenous apoE is cholesterol-rich. Digestion of sphingomyelin with the extracellular enzyme enhances the exogenous apoA-I-mediated cholesterol release to make the HDL cholesterol-rich, but not the endogenous apoE-mediated pathway (14). This result indicated that the behavior of cholesterol molecules in the astrocytes upon HDL assembly with extracellular apolipoprotein is influenced by interaction with sphingomyelin. Thus, intracellular trafficking of cholesterol to link to the exogenous apoA-I-mediated cholesterol release and assembly of HDL might undergo the restriction by sphingomyelin in these cells.

The plasma membrane organizes unique cholesterol/sphingomyelin-rich domains called rafts or caveolae (15). Such domains have indeed been implicated as sites where cellular cholesterol might be leaving the cells (14, 16). Caveolin-1, a 22-kDa protein, is one of the major components of rafts/caveolae that holds a high affinity for cholesterol and sphingomyelin molecules (15, 17). This protein has been shown to be involved in intracellular cholesterol trafficking. It directly binds to cholesterol (18, 19) and induces caveolea domains and their cholesterol enrichment (20). It is also translocated between caveolae and the endoplasmic reticulum by cholesterol oxidation and its removal (21, 22). Caveolin-1 reportedly forms a chaperone complex with heat-shock protein and cholesterol in cytosol to transport newly synthesized cholesterol (19, 23). A more specific role for this protein was demonstrated in the cholesterol transport system to incorporate cholesterol molecules into the HDL generated by apolipoprotein-cell interaction (24, 25).
FIG. 1. Synthesis and translocation to the cytosol of cholesterol and phospholipid in the rat astrocytes treated with apoA-I. A and B, translocation of the lipid. Rat astrocytes were pulse-labeled for 30 min with 40 \( \mu \)Ci of \([3H]\)acetate in 1 ml of F-10 containing 0.02% BSA for 30 min. After washing three times with buffer A (see "Experimental Procedures"), the cells were incubated with (closed circles) or without (open circles) 5 \( \mu \)g/ml apoA-I in 0.02% BSA/F-10 containing 1 mM sodium acetate for the indicated time. Lipid was extracted with the chloroform/methanol (2:1) or the hexane/isopropyl alcohol (3:2) solution from the cytosol fraction (A) or the membrane fraction (B), respectively. The radioactivity of cholesterol was determined after separation by TLC. C–E, rat astrocytes were pulse-labeled with 40 \( \mu \)Ci/ml of \([3H]\)acetate for 120 min. The cells were incubated with (closed circles) or without (open circles) apoA-I (5 \( \mu \)g/ml) and were chased with 1 mM cold acetate for the indicated time. Lipid was extracted from the cytosol, and radioactivity was determined. C (chol), cholesterol; D (pc), phosphatidylcholine; E (spm), sphingomyelin. F–H, the rat astrocytes were pretreated with apoA-I (5 \( \mu \)g/ml) for the indicated time (0–180 min), washed, and incubated with 40 \( \mu \)Ci/ml \([3H]\)acetate for 60 min. Lipid was extracted from the whole cells after washing four times. F (chol), cholesterol; G (pc), phosphatidylcholine; H (spm), sphingomyelin. The data represent the average \( \pm \)S.E. of triplicate assays. *, \( p < 0.01 \) from the control by Student’s \( t \) test.

Based on these findings, we investigated the mechanism by which caveolin-1 mediates cholesterol trafficking to the cellular surface stimulated by the apolipoprotein-cell interaction to generate HDL in rat astrocytes. We discovered that newly synthesized cholesterol was translocated to the cytosol fraction prior to its appearance in the generated HDL, apparently forming a complex with phospholipid accompanied by the increase of caveolin-1 in the cytosol.

EXPERIMENTAL PROCEDURES

Materials—ApoA-I was isolated from freshly prepared human HDL by delipidation and anion-exchange chromatography according to a previously described method (26). Astrocytes were prepared from the brain of day-17 Wistar rat fetus according to the method previously described (5, 27, 28). The cells were seeded and cultured in 10% fetal calf serum/F-10 medium for 1 week.

Radioisotope Labeling of Cellular Cholesterol and Phospholipid—The rat astrocytes at the confluent stage were pulse-labeled with \([3H]\)acetate acid (PerkinElmer Life Sciences) for 30 or 120 min and chased with a medium containing 1 mM cold acetic acid and 0.02% bovine serum albumin (BSA). Alternatively, cellular cholesterol was labeled by incubating with low-density lipoprotein containing \([3H]\)cholesterol for 24 h as previously described (5). Cytosol Preparation and Density Gradient Ultracentrifugation Analysis—The cytosol of rat astrocytes was prepared according to the method of Thom et al. (29). Briefly, the cells pretreated with or without apoA-I in F-10 medium containing 0.02% BSA were harvested with a rubber policeman after washing with 53.6 mM sodium phosphate-bicarbonate buffer, pH 7.4, containing 135 mM NaCl, 2.7 mM KCl, and 5.5 mM glucose (buffer A) four times. The cell pellet from centrifugation at 1,000 rpm for 10 min was treated with cold extract solution composed of 0.02 M boric acid, 0.3 mM EDTA, 1 mM phenylmethylsulfonyl fluoride, and 1 mM benzamidine, pH 10.0, for 15 min with 25 agitation for 10 s every

FIG. 2. Release by apoA-I of newly synthesized lipid from rat astrocytes. Rat astrocytes were pulse-labeled with 40 \( \mu \)Ci/ml \([3H]\)acetate for 120 min. The cells were immediately washed, chased, and treated with (closed circles) or without (open circles) apoA-I (5 \( \mu \)g/ml) for the indicated time. Lipid was extracted from the conditioned medium after the removal of cell debris by centrifugation at 15,000 rpm for 1 h. Radioactivity was counted in cholesterol (A, chol), phosphatidylcholine (B, pc), and sphingomyelin (C, spm) after separation by TLC. Each data point represents the average \( \pm \)S.E. of the triplicate assays. *, \( p < 0.01 \), significantly different from the control by Student’s \( t \) test.
with 2 ml of chloroform/methanol solution (2:1, v/v) five times for assay. Fractions were scraped, and lipid was extracted from each sample from the whole cell with hexane/isopropyl alcohol (3:2, v/v) and centrifuged at 3,000 rpm for 10 min. After removal of nuclei and cell debris, the suspension was centrifuged at 300,000 rpm for 90 min (7). The suspension was neutralized with 0.5 N HCl and was then centrifuged at 90,000 rpm for 1 h in a Hitachi CS 120GX centrifuge. Twelve fractions were collected from the bottom, and each fraction was analyzed for cholesterol content and protein under the same conditions in order to achieve better separation in the fractions of higher density.

**Analysis of Lipid**—After cellular lipid was labeled, lipid was extracted from the whole cell with hexane/isopropyl alcohol (3:2, v/v) and from various cell fractions and culture medium with chloroform/methanol (2:1). Extraction efficiency of the lipid was estimated as 0.895 from the cell and its fractions and from the medium, respectively, by using internal standards. The extract was separated by thin layer chromatography (TLC), and radioactivity in each fraction, such as cholesterol, phosphatidylcholine, and sphingomyelin, was determined (5, 8). For mass assay, total and free cholesterol and triglyceride were directly determined by enzymatic assay methods. For choline phospholipid, the extracted lipid was separated by TLC with a developing solvent of chloroform/methanol/acetic acid/water (25: 15:4:2) and was then enzymatically determined. Phosphatidylcholine (egg, Avanti Polar Lipids, 0–20 μg/spot) and sphingomyelin (bovine brain, Sigma-Aldrich, 0–10 μg/spot) were applied and separated on the same plate as the standards, for chromatography and quantitative assay. Fractions were scraped, and lipid was extracted from each sample with 2 ml of chloroform/methanol solution (2:1, v/v) five times for enzymatic assay of choline phospholipid (5, 8).

**RESULTS**

The cells were metabolically pulse-labeled by incubating with [3H]acetate for 30 min or 120 min and then incubated with apoA-I. Radioactivities in cholesterol, phosphatidylcholine, and sphingomyelin were monitored in the cytosol and membrane fractions. After 30 min of pulse-labeling, the radioactivity profile of cholesterol in the cytosol fraction demonstrated that the transient increase has a peak at 90 min in the apoA-I-treated astrocytes (Fig. 1A). On the other hand, the increase of choles-
The fraction was isolated as the density 1.09–1.16 g/ml and then as a floating fraction in the density 1.18 g/ml from the cytosol of the astrocytes preincubated with and without apoA-I (5 μg/ml) for 90 min. Lipid was analyzed by using enzymatic assay systems. Total and free cholesterol, choline-phospholipid, and triglyceride were directly determined for the whole preparation. Cholesteryl ester was estimated by subtracting free cholesterol from total cholesterol. Lipid was extracted and separated by TLC, and choline-phospholipid was measured for the TLC fractions of phosphatidylcholine and sphingomyelin by referring to the internal standard. The values represent the average ± S.E. of the triplicate samples, standardized as μg of lipid per mg of original cytosol protein.

| PC<sup>a</sup> | SPM<sup>b</sup> | FC<sup>c</sup> | CE<sup>d</sup> | TG<sup>e</sup> |
|---------------|----------------|-------------|-----------|-------------|
| apoA-I(−)     | 4.93 ± 1.25    | 0.87 ± 0.22 | 0.70 ± 0.17 | ND          |
| apoA-I(+)     | 5.63 ± 0.43    | 0.93 ± 0.07 | 0.83 ± 0.09 | ND          |

<sup>a</sup> PC, phosphatidylcholine.
<sup>b</sup> SPM, sphingomyelin.
<sup>c</sup> FC, free cholesterol.
<sup>d</sup> CE, cholesteryl ester.
<sup>e</sup> TG, triglyceride.

<sup>ND</sup>, not detected.

The cytosol was analyzed by density gradient ultracentrifugation to examine the status of lipid translocated to the cytosol by the apoA-I stimulation. When the cells pulse-labeled for 120 min were incubated with apoA-I, only a low lipid count was detected in fractions 3–6 at around 1.12 g/ml (at 60 min) without a significant difference with or without apoA-I. At 90 min, a substantial increase in the count was induced by apoA-I in cholesterol, phosphatidylcholine, and sphingomyelin at the same position of density (Fig. 3, B, D, and F). Fractions 3–6 with a cytosol density of 1.09–1.16 g/ml were collected and examined with an electron microscope using a negative-staining technique. As shown in Fig. 4, somewhat amorphous lipid particles were observed regardless of the incubation with and without apoA-I. The average diameters of the particles were 17.7 ± 7.0 nm and 17.1 ± 6.8 nm with and without apoA-I, respectively. This cytosol fraction was further analyzed for chemical composition of lipid (Table I). Major lipid components were phosphatidylcholine, sphingomyelin, and cholesterol, but a small amount of triglyceride was also detected. The results show that small lipid particles are present in the cytosol, regardless of the stimulation by apoA-I. Translocation of the newly synthesized lipid to these particles was induced by the reaction to extracellular apoA-I. The lipid particles were likely to be complexed with protein as judged by the density. Fig. 5 demonstrates the increase of the activated SREBP1 and SREBP2 in the nuclear fraction by apoA-I. SREBP1 increased somewhat earlier than SREBP2. Translocation of newly synthesized cholesterol is thus associated with stimulation of cholesterol biosynthesis and other sterol-related metabolic pathways via the SREBP-mediated mechanism.

The cytosol preparation was analyzed for protein in density gradient ultracentrifugation (Fig. 6). Regardless of the stimulation by apoA-I, caveolin-1 and cyclophilin A were recovered in the fractions with densities of 1.103–1.148 g/ml (Fig. 6A), equivalent to those of lipid (Fig. 3) and were separated from Bip/GRP78 (an endoplasmic reticulum marker protein). The increase of caveolin-1, but not cyclophilin A, was demonstrated in these fractions by stimulation of the cells with apoA-I (Fig. 6A). Cytosolic caveolin-1 (1.102–1.146 g/ml) was also separated from organelle membrane marker proteins EEA1 (an early endosome marker protein) and GM130 (a Golgi apparatus protein) (Fig. 6B). Heat-shock proteins, HSP 70, 90, and 110 were found in the fractions with higher density. A time-dependent increase of caveolin-1 in the cytosol was synchronized with the translocation of the lipids, reaching a maximum at 60–90 min, whereas cyclophilin A did not show a time-dependent change (Fig. 6C).

To examine whether the cytosol particles identified are distinct from the DRM fraction rich in caveolin-1, DRM and the cytosol particles were directly compared (Fig. 7). The density range of DRM was 1.02–1.10 g/ml where the main protein peak, cholesterol, caveolin-1, and flotillin (another DRM marker) were simultaneously recovered. The cytosol lipid particles were recovered at 1.10–1.16 g/ml with caveolin-1 separated from the main cytosol protein peak (Fig. 7, A and B). The lipid particles in the cytosol were sensitive to Triton X-100, apparently with loss of their original integrated structure, suggesting that the particles were not derived from the DRM domain of the plasma membrane (Fig. 7C).
When Cs-A, a ligand to cyclophilin proteins, was added to the cells, the increase of caveolin-1 in the cytosol by apoA-I was completely suppressed (Fig. 8A). The effects of Cs-A were also examined with regard to cholesterol synthesis, its translocation into the cytosol, and lipid release into the medium by apoA-I. As demonstrated in Fig. 8B, all of the intracellular reactions induced by apoA-I were completely inhibited by Cs-A, and the cholesterol release was substantially suppressed. The results thus suggested that the apoA-I-mediated intracellular events are seemingly related to cholesterol transport to the HDL assembly site.

FIG. 6. Increase of caveolin-1 in the cytosol by apoA-I. A, density distribution of cytosol protein. Astrocytes were treated with (5 μg/ml) and without apoA-I for 90 min, and the cytosol fraction (0.7 mg of protein/7 ml) was collected and analyzed by density gradient ultracentrifugation by overlaying the 7-ml cytosol fraction on top of 18 ml of sucrose solution of density 1.18 g/ml. The samples were collected from the bottom for 12 fractions, and each fraction was analyzed by immunoblotting using specific antibodies against rat caveolin-1 (N-20), cyclophilin A, and Bip/GRP78. B, density gradient analysis of the cytosol of the untreated cells. The cytosol was prepared (1.5 mg of protein/7 ml) and analyzed by the same density gradient ultracentrifugation. Each of the 12 fractions was analyzed for EEA1, Bip/GRP78, GM130, HSP110, HSP90, HSP70, caveolin-1, and cyclophilin A. C, time-dependent change in caveolin-1 in the cytosol. After incubation of the cells with 5 μg/ml of apoA-I for the indicated time, the cells were washed, and the cytosol was collected. The proteins (30 μg/lane) were analyzed by immunoblotting. D, density gradient profiles for the experiments shown in A and B.
ApoA-I Induces Caveolin/Cholesterol/Translocation

The translocated lipids to the cytosol appear to form particles having a density of the lipid-protein complex. Caveolin-1 and cyclophilin A also seem to associate with lipid in the cytosol, being distinct from the endosome and the microsomal derived from the endoplasmic reticulum/Golgi apparatus. EEA1, GM130, and Bip/GRP78 were recovered in higher density fractions than the lipid-protein complex particles as well as the HSPs (Fig. 6). It is also obvious that the particles are not derived from the DRM domain or caveolae because of their sensitivity to Triton X-100 (Fig. 7). Biosynthesis of cholesterol and phospholipids appears to be enhanced after this translocation, presumably triggered by the decrease of cholesterol in the SREBP-sensitive compartment. The labeled lipids appear in the HDL extracellularly assembled by apoA-I after their translocation into the cytosol.

Because caveolin-1 has been proposed to mediate intracellular cholesterol transport to the cellular surface, which is linked to cholesterol release by apoA-I, it is conceivable that this particle may function to carry cholesterol and other lipids to the cell surface site where HDL assembly takes place. It has been reported that the movement of newly synthesized cholesterol to the plasma membrane is accompanied by the formation of the protein complex composed of caveolin-1, cyclophilin A, cyclophilin 40, and heat-shock protein 56 in the cytosol of NIH 3T3 cells and also lymphoid cell line L1210-JF transfected by caveolin-1 (23). In the case of rat astrocytes, however, cyclophilin 40 was recovered in the membrane fraction and the higher density protein fraction of the cytosol, but not in the lipid-caveolin-1 fraction. Whereas such a proposed protein complex reportedly contains only cholesterol as a lipid component, the lipid-protein complexed particles identified in the rat astrocyte cytosol in this study contained cholesterol, phosphatidylcholine, and sphingomyelin. ApoA-I induced incorporation of newly synthesized cholesterol and phospholipid into these particles. Although both caveolin-1 and cyclophilin A seem to be associated with these particles in a density gradient analysis, an anti-caveolin-1 antibody failed to coprecipitate cyclophilin A with caveolin 1 from the rat astrocytes cytosol.

Intracellular cholesterol distribution has been shown to be greatly dependent on the function of caveolin-1 and caveolae. Expression of caveolin-1 is closely related to cellular cholesterol levels (24, 31). Exposure of human fibroblasts to cholesterol oxidase rapidly allows caveolin-1 to redistribute from the plasma membrane to the endoplasmic reticulum and then to the Golgi complex (21). The newly synthesized cholesterol was first moved from the endoplasmic reticulum to caveolae linked to the caveolin-1 movement and then to the noncaveole domain of the plasma membrane (32). Cholesterol transport from the endoplasmic reticulum to the plasma membrane is greatly enhanced in caveolin-1-transfected lymphocytes (23). Down-regulation of caveolin-1 reduced the incorporation of cholesterol into HDL assembled by the cell-apoA-I interaction (24, 25).

Thus, it may be irrelevant to conceive that the cytosolic caveolin-lipid complex in rat astrocytes may function as a vehicle for transport of cholesterol and phospholipid from the endoplasmic reticulum to the DRM domain of the plasma membrane.

ABCA1 plays a key role in the apolipoprotein-mediated HDL assembly (11–13), but an exact mechanism must still be determined. Physical interaction of apolipoprotein with the cell surface seems to require ABCA1 (33, 34), and the reaction primarily mediates assembly of HDL with cellular phospholipid (25, 35, 36). Cholesterol enrichment in the HDL, thus generated, is regulated in a relatively independent manner from the assembly of HDL particles (9), and caveolin-1 seems involved in this step (25). This part is also dependent on sphingomyelin-chole-

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Footnote: ² J. Ito and S. Yokoyama, unpublished data.
ApoA-I Induces Caveolin/Cholesterol/Translocation

7935
terol interaction in DRM in astrocytes (14) so that intracellular cholesterol transport by caveolin-1 may enrich this domain with cholesterol to lead to its incorporation into the HDL. More studies are required to prove this hypothesis.

Anderson and co-workers (37) have reported that exocrine cells that synthesize both apoA-I and apoE secreted caveolin-1 along with these apolipoproteins as a lipoprotein particle. They have suggested that caveolin-1 with apolipoproteins are present as a lipoprotein in the endoplasmic reticulum/Golgi compartment and are transported in the secretory pathway. In contrast, neither caveolin-1 was detected in the HDL fraction in the medium of the rat astrocytes pretreated with apoA-I nor was endogenous apoE in the caveolin-lipid complex of the cytosolic fraction of the rat astrocytes. Therefore, cholesterol trafficking for its release in the HDL assembly reaction with extracellular apolipoprotein seems essentially different from what was observed in the exocrine cells. The absence of apoE in the cytosolic fraction excludes the possibility that the HDL particles in the secretory pathway, if any, contaminated the isolated fraction. More recently, the same group demonstrated the presence of caveolin-1 and cyclophilin A in an HDL density fraction of the cytosol of human fibroblasts (38), so the present findings may not be specific for astrocytes but rather more generally applicable for the HDL assembly system by apolipoprotein and cellular lipid.

The results of inhibition of the apoA-I-mediated cholesterol release and other cellular reactions by Cs-A support the hypothesis that the translocation of lipid and caveolin-1 to the cytosol is associated with lipid release and HDL assembly by apoA-I. The results also suggest that the reactions are dependent on the function of cyclophilin proteins.

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