Cholesterol and Plant Sterol Efflux from Cultured Intestinal Epithelial Cells Is Mediated by ATP-Binding Cassette Transporters

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In this study, we analyzed functions of ATP-binding cassette (ABC) transporters involved in sterol transport from Caco-2 cells. Treatment with a synthetic liver x receptor ligand elevated both mRNA and protein levels of ABCG5, G8, and ABCA1. The ligand stimulated cholesterol efflux, suggesting that ABC transporters are involved in it. To identify the acceptors of cholesterol, potential molecules such as apolipoprotein A-I, glycocholic acid, phosphatidylcholine, and bile acid micelles were added to the medium. Apo A-I, a known acceptor of cholesterol transported by ABCA1, elevated cholesterol efflux on the basal side, whereas the others raised cholesterol efflux on the apical side. Moreover, bile acid micelles preferentially augmented plant sterol efflux rather than cholesterol. Finally, in HEK293 cells stably expressing ABCG5/G8, bile acid micelle-mediated sterol efflux was significantly accelerated. These results indicate that ABCG5/G8, unlike ABCA1, together with bile acids should participate in sterol efflux on the apical surface of Caco-2 cells.

Key words: ATP-binding cassette transporter G5/G8; intestinal sterol excretion; cholesterol; plant sterol; Caco-2 cell

Elevated levels of low density lipoprotein (LDL) and reduced levels of high density lipoprotein (HDL) in plasma are associated with the risk of developing atherosclerosis.1–3 Intestinal cholesterol absorption can influence plasma cholesterol levels4 and treatment with Ezetimibe, an inhibitor of cholesterol absorption in the intestine, decreases plasma LDL-cholesterol concentrations by 20%.5 Furthermore, cholesterol secretion back into the intestinal lumen is also considered to influence plasma cholesterol levels by regulating net cholesterol absorption from the intestine and incorporation of cholesterol into the body. Thus, regulation of intestinal cholesterol absorption and excretion might provide an effective approach to prevent the development of atherosclerosis, but the molecular mechanism underlying cholesterol absorption and excretion in the intestine remains to be elucidated.

ABCG5 and G8, members of the ABC transporter family, are mainly expressed in the liver and intestine, and are thought to work as a sterol efflux heterodimer pump for cholesterol, plant sterols, and other natural non-cholesterol sterols.6,7 They are believed to localize on the apical membrane of hepatocytes or the brush border membrane of the intestine.8,9 In cells these proteins are heterodimerized and glycosylated in endoplasmic reticulum, and then a matured heterodimer is transported to the cell surface to function as a sterol pump.10–12 Mutations in ABCG5/G8 cause the rare genetic disorder sitosterolemia, characterized by accumulation of cholesterol and plant sterol in blood and tissues.13,14 ABCG5/G8 deficient mice (G5G8-/-) show a decrease in biliary cholesterol and plant sterol secretion from the liver and an increase in plant sterol absorption in the intestine, whereas human ABCG5/G8 transgenic mice show an opposite phenotype.16 These findings suggest that ABCG5/G8 stimulate biliary sterol secretion from the liver and suppress intestinal sterol absorption due to enhanced sterol efflux into the intestinal lumen.

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Abbreviations: ABC, ATP-binding cassette; LXR, liver x receptor; apoA-I, apolipoprotein A-I; GCA, glycocholic acid; PC, phosphatidylcholine; LDL, low-density lipoprotein; HDL, high-density lipoprotein; GDCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; TCA, taurocholic acid; TDCA, taurodeoxycholic acid; TCDCA, taurochenodeoxycholic acid

It has been reported that net cholesterol absorption correlates with the expression levels of ABCG5/G8 in the jejunum and ileum but not in the duodenum in mice, but the direct relationship between intestinal ABCG5/G8 and sterol efflux has not been elucidated. It is possible that the reduced plant sterol absorption observed in ABCG5/G8 transgenic mice may be due to elevated sterol secretion into the bile, not to a direct reduction in sterol absorption in the intestine. In humans ABCG5/G8 are indeed predominantly expressed in the liver rather than the intestine. To investigate the role of ABCG5/G8 in the intestine, we used differentiated human colon carcinoma Caco-2 cells as a model of intestinal epithelial cells. First, we examined the effects of a synthetic LXR ligand on the expression of ABCG5 and G8 and also sterol efflux both into the apical (intestinal lumen side) and basal side (basolateral membrane side) from polarized Caco-2 cells cultured on filter membranes. Next we determined potential acceptors of sterols secreted into the apical medium. Further, we investigated the preferential efflux of cholesterol and a plant sterol, β-sitosterol, into either the apical or basal side. Finally, we analyzed the role of ABCG5/G8 in regulatory sterol efflux using HEK293 cells that stably expressed both ABCG5 and G8.

Materials and Methods

Materials. [3H]-cholesterol and [14C]-β-sitosterol were obtained from GE Healthcare(Chicago, IL). Bile acid sodium salts, oleic acid, phosphatidylcholine were from Sigma (St. Louis, MO). Apolipoprotein A-I was from Calbiochem. Anti-ABCA1 and -ABCG8 antibodies were from Novus Biologicals (Littleton, CO). Other general chemicals were from Sigma-Aldrich, Wako Pure Chemical Industries (Osaka, Japan), and Nacalai Tesque (Kyoto, Japan). TO901317 was obtained from Sigma.

Cell culture. Human colon carcinoma cell line Caco-2 cells were obtained from the Riken cell bank (Tsukuba, Japan). Caco-2 cells were grown in Dulbecco’s modified Eagle’s medium (DMEM) (Sigma), 10% fetal bovine serum (FBS), and 1% non-essential amino acids solution (Sigma) at 37°C under a 5% CO2 atmosphere. Cells cultured for 2 weeks (10 d after 100% confluency) were considered to be differentiated. HEK293 cells were grown in DMEM with 10% FBS at 37°C under a 5% CO2 atmosphere.

Stable cell line. Expression vectors for ABCG5 and ABCG8 were constructed by inserting the fragments for human ABCG5 and ABCG8 respectively into pcDNA3.1(+). HEK293 cells were transfected with expression plasmids, pcDNA3.1-ABCG5 and pcDNA3.1-ABCG8, with LipofectAMINE (Invitrogen, Carlsband, CA) according to the manufacturer’s instructions. The cells were cultured with a selection medium containing 1.0 mg/ml genetin (G418), and surviving clonal cells were collected. The expression of ABCG5 and G8 were examined by Western blotting.

RNA isolation and quantitative PCR. Caco-2 cells were cultured on Transwell membrane (Corning, Acton, MA) in 6-well culture dishes at a density of 6.0 × 10^6/well and cultured for 2 weeks. The cells were washed with PBS, scraped from the Transwell membrane, and centrifuged at 1,000 × g for 10 min. Total RNA was isolated using an RNA preparation kit (Isogen, Nippon Gene, Tokyo). The reverse transcription reaction was performed using SuperScript III (Invitrogen). Quantitative real-time PCR was performed using TaqMan universal PCR master mix (For ABCA1, ABCG5, and ABCG8) and SYBR green PCR master mix (for 36B4). Quantitative PCR analysis was conducted on the ABI 7000 sequence detection system (Applied Biosystems, Foster City, CA). Assay on Demand PCR primers were human ABCA1 (Hs00194045_m1); human ABCG5 (Hs00223686_m1); human ABCG8 (Hs00223690_m1) (Applied Biosystems). PCR primers for human 36B4 were 5'-CTGATCATCAGCAGGTGTT-3' and 5'-CCAGGAAGCCCTGACCTTT-3'. The results were standardized with 36B4 as an internal control gene. Assays were performed in triplicate and the results were expressed as mean ± standard error.

Western blot analysis. Caco-2 cells were cultured on Transwell membranes in 6-well culture dishes at a density of 6.0 × 10^6/well for 2 weeks. HEK293 cells were cultured in 6-well culture dishes for 1 d. The cells were harvested and suspended in 10 mM HEPES buffer containing 1.5 mM MgCl2, 10 mM KCl, 1.0 mM EDTA and 1% of protease inhibitor cocktail (Sigma). After homogenization, cell lysates were centrifuged at 1,000 × g for 10 min at 4°C, and the supernatants were ultra-centrifuged at 100,000 × g for 30 min at 4°C to obtain microme fractions. The precipitates were solubilized in 50 mM Tris buffer containing 2% SDS, 100 μM DTT, and 1% protease inhibitor cocktail and subjected to sodium dodecyl sulfate (SDS) -6% polyacrylamide gel electrophoresis (PAGE). Proteins were transblotted onto PVDF membrane (Millipore Corp., Bedford, MA). Western blot analysis was carried out using rabbit polyclonal antibodies against human ABCA1 and ABCG8 (Novus Biologicals, Littleton) and mouse monoclonal antibody against human ABCG5 with chemiluminescent substrate (ECL Plus, Amersham Bioscience). The signals were quantified with a Luminofmager (LAS-3000, Fuji Film, Tokyo).

Preparation of bile acid-containing micelle. Bile acid containing micellar solutions were prepared as described previously. Briefly, 0.6 mM of phosphatidylcholine (PC), 1.0 mM of oleic acid, and 6.6 mM of bile acid sodium salt were resolved in DMEM and sonicated. Mixed micellar solutions were prepared when added to...
culture medium. Following bile acid sodium salts were used: glycocholic acid (GCA), glycodeoxycholic acid (GDCA), glycochenodeoxycholic acid (GCDC), taurocholic acid (TCA), taurodeoxycholic acid (TDCA), taurochenodeoxycholic acid (TCDC). 

Sterol efflux assays. Caco-2 cells were cultured on polycarbonate semipermeable Transwell membranes with 0.4 μm pores (Coster, Cambridge, MA) at a density of 2.0 x 10⁶/well in 12-well culture membrane for 2 weeks. The differentiated and polarized Caco-2 cells were labeled with [³H]-cholesterol or [³H]-β-sitosterol (0.5 μCi/well) for 24 h in DMEM containing 10% FBS. The medium was removed and the cells were washed and incubated for 45 min with an FBS-free DMEM (pre-incubation period). Then the cells were incubated with a serum-free chase DMEM containing 1% of serum-free incubation period). The media in both the apical and the basolateral chamber were collected and centrifuged at 15,000 rpm for 10 min to obtain the supernatants. The cells, washed with PBS 3 times, were harvested and lysed in 0.1% TritonX-100-PBS. ³H-radioactivities secreted in the media and retained in the cells were measured with a scintillation counter. The cholesterol efflux rate was calculated by dividing the radioactivities in the media by total radioactivities in the cells plus media (apical plus basolateral medium). Assays were performed in triplicate and the results were expressed as mean ± standard error.

HEK293 cells stably expressing ABCG5/G8 cells were cultured on 6-well plates at a density of 1.0 x 10⁶ cells, and incubated for 24 h. The cells were labeled with [³H]-cholesterol or [³H]-β-sitosterol (2.0 μCi/well) for 24 h, and then further incubated as described above. The cholesterol efflux rate was calculated by dividing the radioactivities in the media by total radioactivities in the cells plus media. Assays were performed in triplicate and the results were expressed as mean ± standard error.

Statistical analysis. Values are presented as mean ± standard error. Statistical significance was determined by Student’s t-test. A value of P < 0.05 was considered statistically significant.

Results

An LXR synthetic ligand, TO901317, augmented sterol efflux from differentiated Caco-2 cells as well as gene and protein expression of ABC transporters

To investigate ABC transporter-mediated sterol efflux from intestinal epithelial cells, we first tried to induce ABC transporter expression in differentiated Caco-2 cells by the use of a synthetic ligand of LXR, which has been reported to stimulate gene expression of ABCA1, G5, and G8. 18-20) Figure 1A shows a tendency to the effect that ABCA1, G5, and G8 gene expression were gradually elevated with an increase in the concentration of TO901317. The protein levels of ABCA1, G5, and G8 increased in the presence of 1 to 10 μM of TO901317 (Fig. 1B). According to the results shown in Fig. 1B, Caco-2 cells were treated with 1 μM TO901317 to induce ABC transporter protein expression in the subsequent experiments. Next we measured sterol efflux from the apical or the basolateral surface of Caco-2 cells cultured on Transwell plates in the presence or absence of TO9091317. Two to seven percent of total cellular radioactivity uptaken during the pulse period (24 h) was recovered in the upper (apical) or lower (basolateral) chamber during the chase period of 24 hrs (Fig. 1C). In the presence of TO901317, cholesterol efflux into both sides significantly elevated. On the other hand, TO901317 stimulated β-sitosterol efflux only into the apical side.

Bile acid-containing micelle is a possible acceptor of sterols pumped out from the apical surface of Caco-2 cells

Apo A-1-mediated cholesterol efflux due to ABCA1 has been well characterized. 21) To determine which side of polarized Caco-2 cells ABCA1 works on, cholesterol efflux was analyzed when apo A-1 was exposed to cells from the apical or the basolateral surface (Fig. 2A). Apo A-1 exposure only from the basolateral surface stimulated cholesterol efflux from the Caco-2 cells, suggesting that ABCA1 should work on the basolateral surface. On the other hand, the addition of GCA or PC in the upper chamber medium (the apical side) significantly raised cholesterol efflux from the apical side. The concentration of GCA (1 mM) was determined based on a report on human intestinal contents 22) and our finding that the higher concentration was toxic to cultured Caco-2 cells. A significant decrease in cholesterol efflux from the basal side in the presence of GCA (in the middle panel of Fig. 2A) remains unexplainable. These results indicate that ABC transporters other than ABCA1 should function on the apical surface of differentiated Caco-2 cells to transport intracellular cholesterol. Next we examined whether bile acid-containing micelle preformed with PC and olate, which is thought to be a more likely form of bile acids in the intestinal lumen, 23) works as a potent acceptor. As Fig. 2B shows, preformed micelles more efficiently promoted cholesterol efflux from Caco-2 cells than non-micelle bile acids (almost 5-fold, 4% vs. 20%).

Bile acid-containing micelle works as an acceptor of β-sitosterol pumped out from the apical surface of Caco-2 cells

Next we determined whether bile acid-containing micelle in the apical medium works as an acceptor for plant sterol and β-sitosterol as well as cholesterol. Further, we compared the functions of conjugated forms of bile acid molecules such as cholic acid (CA), deoxycholic acid (DCA), and chenodeoxycholic acid
The difference between glycocholic acid (GCA) and taurocholic acid (TCA) in the acceptor activity was also compared. As Fig. 3A shows, all forms of micelle examined in the current experiments highly stimulated \( \beta \)-sitosterol efflux into the apical medium. Moreover, the percentage of \( \beta \)-sitosterol recovered in the apical medium was much higher than that of cholesterol in the presence of bile acid micelle, indicating that plant sterol once uptaken in Caco-2 cells is largely pumped out into the apical medium. Moreover, micelle containing conjugated DCA or CDCA rather than conjugated CA more highly enhanced both cholesterol and \( \beta \)-sitosterol efflux into the apical side, but there was no major difference between glycine and taurine conjugated forms.

The results shown in Figs. 1 and 2 indicate that apo A-1 and bile acid-containing micelles stimulate sterol efflux on the basolateral and the apical surface respectively of Caco-2 cells. Indeed, apo A-1 in the blood can access the basolateral surface of intestinal epithelial cells and bile acids also the apical surface of intestinal cells. We next examined sterol efflux into both sides in the presence of these acceptors in the right side, apo A-1 in the basolateral medium and GCA micelle in the apical medium. As Fig. 3B shows, GCA micelle in the apical medium stimulated cholesterol and \( \beta \)-sitosterol efflux only into the apical medium, and apo A-1 in the basolateral medium stimulated only cholesterol efflux.
from the basal side. These results indirectly suggest that ABCA1 should transport cholesterol in an apo A-I-mediated manner on the basolateral surface of Caco-2 cells, and that ABCG5/G8, a potential plant sterol transporter, might work on the apical surface for cholesterol and plant sterol efflux.

**Cholesterol and β-sitosterol efflux from ABCG5/G8 expressing HEK293 cells was stimulated by GCA-containing micelle**

To confirm ABCG5/G8-mediated cholesterol and β-sitosterol efflux, we established a stable cell line expressing this heterodimer transporter. Western blot analysis using specific antibodies recognizing these proteins revealed that these cells express ABCG5/G8 (Fig. 4A). Additional bands with a higher molecular weight than estimated, thought to be highly glycosylated forms, were observed in both western blotting analyses (Fig. 4A, asterisked bands). In the presence of GCA-containing micelle, both cholesterol and β-sitosterol efflux were greatly stimulated in ABCG5/G8 expressing cells, although we observed non-specific diffusion of

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**Fig. 2. Putative Acceptors of Cholesterol Excreted into the Apical and Basal Sides.**

A. Caco-2 cells were cultured on Transwell membranes for 2 weeks and labeled with [3H]-cholesterol for 24 h, and then incubated for the following 24 h with medium containing 10 μg/ml of apolipoprotein A-I (apo A-I), 1.0 mM of glycocholic acid (GCA), or 1 mg/ml of phosphatidylcholine (PC) in either the apical or basal chamber. [3H]-cholesterol radioactivities secreted into the upper chamber (apical) or the lower chamber (basal), in which one of putative acceptors was added, were measured. Results are shown as % of total radioactivities, as described in the Fig. 1 legend. Values are means ± S.E. (n = 3). *, P < 0.05. B. Caco-2 cells were cultured on Transwell membranes for 2 weeks and labeled with [3H]-cholesterol for 24 h, and then incubated for the following 24 h with medium containing 1 mM of GCA or GCA-containing micelle in the apical chamber. Results are shown as % of total radioactivities (radioactivities in the apical chamber/radioactivities in the cells and both chambers). There were no changes in cholesterol efflux into the basal side by these treatments (data not shown). Values are means ± S.E. (n = 3). *, P < 0.05.
sterols from control HEK293 cells in the presence of GCA-containing micelle (Fig. 4B). These results indicate that ABCG5/G8 together with bile acid-containing micelle potentiates transport of cholesterol and \(\beta\)-sitosterol from the cells. These results might account to some extent for the ABCG5/G8-mediated sterol efflux from the apical surface of cultured Caco-2 cells in the presence of an LXR ligand, as shown in Figs. 1 to 3.

**Discussion**

In this study, we report that: i) an LXR synthetic ligand TO901713 stimulated cholesterol and \(\beta\)-sitosterol efflux; ii) bile acid-containing micelle was an acceptor of sterol secreted from the apical surface; iii) \(\beta\)-sitosterol was more efficiently excreted into the apical side than cholesterol in differentiated Caco-2 cells; and iv) ABCG5/G8 mediated both cholesterol and \(\beta\)-sitosterol efflux induced by bile acid-containing micelle, not by apo A-I, from HEK293 cells stably expressing ABCG5/G8. These observations support the thesis that cholesterol and \(\beta\)-sitosterol are excreted from the intestinal epithelial cells into the intestinal lumen by ABCG5/G8. So far we have failed to find direct evidence that ABCG5/G8 predominantly work as a sterol transporter on the apical surface of Caco-2 cells. However, we
present data here bearing out the conclusion that ABCG5/G8 are involved in sterol efflux from intestinal cells back into the apical side to some extent.

Mutations in ABCG5 or ABCG8 cause a rare genetic disorder, sitosterolemia, characterized by elevated plasma plant sterol levels due to increased absorption in the intestine and decreased excretion into the bile in the liver.13,14) Studies of genetically manipulated mice indicate that ABCG5/G8 is a key transporter mediating cholesterol and plant sterol secretion into the bile.15,16) It has been reported that ABCG5/G8 is required for biliary cholesterol secretion according to experiments with ABCG5/G8 transgenic mice24) and liver-specific ABCG5/G8 transgenic mice.25) At present, the possibility that ABCG5/G8 in the intestine modulates cholesterol and plant sterol absorption by mediating sterol excretion to the intestinal lumen as observed in bile formation in the liver has not been established as fact. Duan L-P et al. reported that ABCG5 and G8 mRNA expression in the jejunum and the ileum, but not in the duodenum, are major determinants for cholesterol and plant sterol secretion in mice, and suggested that cholesterol absorption is regulated by the functions of ABCG5 and G8 expressed in these regions.26) However, it has been demonstrated that the relative expression levels of ABCG5/G8 in the intestine and the liver differ among species. In mice, ABCG5/G8 are expressed more in the intestine than in the liver whereas they are more abundant in the liver in humans.14) Langheim et al. discussed the possibility that ABCG5/G8 reduce the absorption of sterol directly by promoting sterol excretion from the enterocytes and indirectly by increasing biliary sterol secretion by reference to human ABCG5/G8 transgenic mice in which ABCG5/G8 were highly expressed in the liver as in humans.27) So far all these reports merely speculated on the biological functions of ABCG5/G8 in the intestine. The current study might be one of the first reports providing direct evidence of sterol efflux through these transporters together with bile acid-containing micelle.

To date, no LXR binding sites have been found in the sitosterolemia locus, STSL, which is comprised of ABCG5 and G8.28) However, an LXR ligand has been shown to increase ABCG5 and G8 gene expression in mouse liver and intestine and in rat hepatoma cells.18,29) In addition, in LXRβ-deficient mice, ABCG5 and G8 gene expression was not up-regulated by feeding of a cholesterol-rich diet, unlike the increase observed in wild-type mice.18) It is well established that LXR synthetic ligands up-regulate ABCA1 gene expression in the intestine30,31) and sterol efflux in Caco-2 cells.32,33) Our data also demonstrate that an LXR synthetic ligand,

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**Fig. 4.** Cholesterol and β-Sitosterol Efflux Mediated by ABCG5/G8.

A, HEK 293 cells stably expressing ABCG5/G8. Total membrane fractions were prepared and subjected to western blot using ABCG5 and ABCG8 antibodies. B, HEK 293 cells and stable cells (ABCG5/G8) were labeled with [3H]-cholesterol or [3H]-β-sitosterol for 24 h, and then incubated with or without 0.5 mM of GCA-containing micelle in the apical chamber for the following 24 h. Cholesterol and β-sitosterol efflux into the apical side were calculated. Results are shown as % of total radioactivities. Values are means ± S.E. (n = 3). *, P < 0.05.
The data presented herein show that the absorption of sterols in the intestine is largely independent of the species. In contrast, ABCA1 was reported to localize on the basolateral membrane of Caco-2 cells. The current findings that apo A-I-mediated cholesterol efflux induced by an LXR ligand occurred on the basolateral side of Caco-2 cells, and that bile acid-mediated cholesterol/plant sterol efflux from the apical side was promoted by the same ligand reflect the intracellular localization of these transporters.

The molecular mechanism by which ABCA1 together with apo A-I transports cholesterol and phospholipids to generate nascent HDL particles has been widely accepted. Therefore, we strongly believe that the apo A-I-mediated cholesterol but not plant sterol (data not shown) efflux from the basolateral surface of differentiated Caco-2 cells observed in the current study is predominantly driven by functions of ABCA1. On the other hand, in the case of cholesterol and plant sterol efflux occurring on the apical surface, we cannot rule out the possibility that some transporters other than ABCG5/G8 might be involved in it. The results presented in Fig. 4 clearly indicate that ABCG5/G8 exogenously expressed in HEK293 cells enhance cholesterol/plant sterol efflux in the presence of bile acid-containing micelle, whereas sitosterol is less secreted into the apical medium than cholesterol even in the presence of apo A-I (Fig. 3B). These results support the idea that ABCG5/G8 work as a plant sterol excretion-pump in the small intestine, leading to reduced plant sterol net absorption.

In conclusion, this study indicates that apo A-I-mediated cholesterol efflux occurred on the basolateral surface of differentiated Caco-2 cells while bile acids-mediated cholesterol/plant sterol efflux did so on the apical surface. Excretion from both sides was stimulated by an LXR ligand, suggesting that ABCA1 and ABCG5/G8 must work at least partly on the basolateral and apical membranes, respectively. Based on the notion that back-flow of sterols from the intestinal epithelial cells into the lumen can determine sterol net absorption in the intestine, ABCG5/G8 should become a critical target for the regulation of cholesterol metabolism and prevention of atherosclerosis.

References


10) Graf, G. A., Yu, L., Li, W. P., Gerard, R., Tuma, P. L., Cohen, J. C., and Hobbs, H. H., ABCG5 and ABCG8 are obligate heterodimers for protein trafficking and biliary sitosterol is more highly secreted into the apical medium than cholesterol in the presence of bile acid-containing micelle, whereas β-sitosterol is less secreted into the basal medium than cholesterol even in the presence of apo A-I (Fig. 3B).


