

Effect of Antisense Oligonucleotides against Cholesteryl Ester Transfer Protein on the Development of Atherosclerosis in Cholesterol-fed Rabbits*

(Received for publication, September 4, 1997, and in revised form, November 25, 1997)

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Cholesteryl ester transfer protein (CETP) is the enzyme that facilitates the transfer of cholesteryl ester from high density lipoprotein (HDL) to apolipoprotein B (apoB)-containing lipoproteins. However, the exact role of CETP in the development of atherosclerosis has not been determined. In the present study, we examined the effect of the suppression of increased plasma CETP by intravenous injection with antisense oligodeoxynucleotides (ODNs) against CETP targeted to the liver on the development of atherosclerosis in rabbits fed a cholesterol diet. The ODNs against rabbit CETP were coupled to asialoglycoprotein (ASOR) carrier molecules, which serve as an important method to regulate liver gene expression. Twenty-two male Japanese White rabbits were used in the experiment. Eighteen animals were fed a standard rabbit chow supplemented with 0.3% cholesterol throughout the experiment for 16 weeks. At 8 weeks, they were divided into three groups (six animals in each group), among which the plasma total and HDL cholesterol concentrations did not significantly change. The control group received nothing, the sense group were injected with the sense ODNs complex, and the antisense group were injected with the antisense ODNs complex, respectively, for subsequent 8 weeks. ASOR-poly(L-lysine) ODNs complex were injected via the ear veins twice a week. Four animals were fed a standard rabbit diet for 16 weeks. The total cholesterol concentrations and the CETP mass in the animals injected with antisense ODNs were all significantly decreased in 12 and 16 weeks compared with those injected with sense ODNs and the control animals. The HDL cholesterol concentrations measured by the precipitation assay did not significantly change among the groups fed a cholesterol diet, and triglyceride concentrations did not significantly change in the four groups. However, at the end of the study, when the HDL cholesterol concentrations were measured after the isolation by ultracentrifugation and a column chromatography, they were significantly higher in the animals injected with antisense ODNs than in the animals injected with sense ODNs and in the control animals. A reduction of CETP mRNA and an increase of LDL receptor mRNA in the liver were observed in the animals injected with antisense ODNs compared with those injected with sense ODNs and the

control animals. Aortic cholesterol contents and the aortic percentage lesion to total surface area were significantly lower in the animals injected with antisense ODNs than in the animals injected with sense ODNs and in the control animals. These findings showed for the first time that suppression of increased plasma CETP by the injection with antisense ODNs against CETP coupled to ASOR carrier molecules targeted to the liver could thus inhibit the atherosclerosis possibly by decreasing the plasma LDL + very low density lipoprotein (VLDL) cholesterol in cholesterol-fed rabbits.

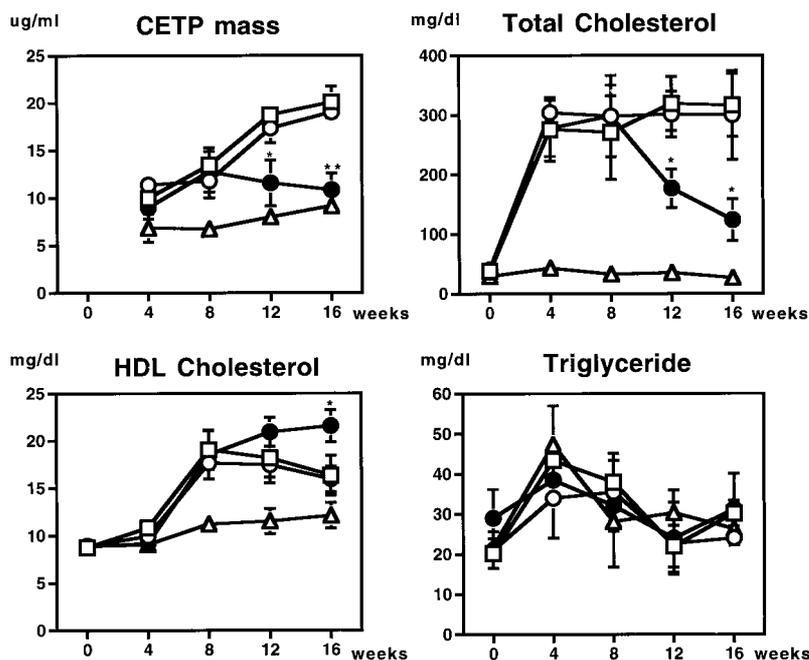
Cholesteryl ester transfer protein (CETP)¹ is a plasma glycoprotein that catalyzes the transfer of cholesteryl ester and triglyceride among lipoproteins (1, 2). The homozygotes for CETP deficiency demonstrated markedly elevated HDL cholesterol and plasma apolipoprotein A-I (apoA-I) levels as well as decreased LDL cholesterol and plasma apoB levels (3, 4). CETP deficiency may be associated with protection against ischemic heart disease, based on the observed longevity (5) as well as the lack of any evidence of coronary heart disease (4). However, recently it was reported that in some patients with CETP deficiency there were increased coronary heart diseases (6–8). Even in the study using CETP transgenic mice, the exact role of CETP in the development of atherosclerosis has yet to be clarified. Marotti *et al.* (9) demonstrated that transgenic mice expressing cynomolgus monkey CETP had significantly more early atherosclerotic lesions in the proximal aorta than controls when fed a high cholesterol diet. On the other hand, more recently Hayek *et al.* (10) concluded that transgenic mice expressing human CETP and apoCIII showed the inhibition of the development of early atherosclerotic lesions. To determine how CETPs affect atherosclerosis in clinical situations, plasma CETP levels must be changed in the experimental models because the studies in the patients with CETP deficiency or CETP transgenic mice go from one extreme to another. We have showed that intravenous injection with antisense oligodeoxynucleotides (ODNs) against CETP coupled to asialoglycoprotein carrier molecules targeted to the liver could inhibit the plasma CETP activity, and as a result, induced a decrease in the plasma LDL + VLDL cholesterol and an increase in the plasma HDL cholesterol in cholesterol-fed rabbits (11). In the present study using an intravenous injection with antisense

* This work was supported in part by a grant-in-aid from the Ministry of Education, Science, and Culture of Japan. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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¹ The abbreviations used are: CETP, cholesteryl ester transfer protein; HDL, high density lipoprotein; apo, apolipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein; ODN, oligodeoxynucleotides; ASOR, asialoglycoprotein; PCR, polymerase chain reaction; HPLC, high performance liquid chromatography.

FIG. 1. Changes in the CETP mass and the plasma cholesterol and triglyceride concentrations in the four groups. The HDL cholesterol concentrations at 16 weeks were measured after the isolation by ultracentrifugation and HPLC. Control □, the rabbits fed only a 0.3% cholesterol diet; Sense ○, the rabbits fed a 0.3% cholesterol diet and injected with sense ODNs; Antisense ●, the rabbits fed a 0.3% cholesterol diet and injected with antisense ODNs; Standard △, the rabbits fed a standard diet. Values are the mean ± S.E. *, $p < 0.05$; **, $p < 0.001$.



ODNs to the liver, we examined the effect of the suppression of increased plasma CETP on the plasma cholesterol concentrations and the development of atherosclerosis in rabbits fed a cholesterol diet.

MATERIALS AND METHODS

Construction of ODNs—The sequences of ODNs against rabbit CETP and asialoglycoprotein-poly(L-lysine) ODNs complex used in this study were same as described previously (11).

Experimental Protocol—Twenty-two male Japanese White rabbits weighing 2.0–2.5 kg were used in the experiment. All animals were housed individually and had free access to water. Eighteen animals were fed a standard rabbit chow supplemented with 0.3% cholesterol for 8 weeks and divided to three groups (six animals in each group), among which the plasma total and HDL cholesterol concentrations did not significantly change. After 8 weeks, the control group again received only a 0.3% cholesterol diet, the sense group had a 0.3% cholesterol diet and were injected with asialoglycoprotein (ASOR)-poly(L-lysine) sense ODNs complex, and the antisense group also had a 0.3% cholesterol diet and were injected with ASOR-poly(L-lysine) antisense ODNs complex; all animals were fed until 16 weeks. Four animals were fed a standard rabbit diet for 16 weeks (standard group). ASOR-poly(L-lysine) antisense ODNs complex were injected via the ear veins twice a week. The amount of ODNs injected was 30 $\mu\text{g}/\text{kg}$ for each rabbit. Every 4 weeks, about 1 ml of the blood was drawn from all the animals via their ear veins. At the end of the study, all rabbits were sacrificed, and liver specimens, aorta, and blood samples were taken.

Measurement of mRNAs in Liver—Total RNA was isolated from the liver, and the rabbit-labeled cDNA probes for CETP and glyceraldehyde-3-phosphate dehydrogenase mRNA were produced by the nonradiolabeled reverse transcription-polymerase chain reaction (PCR) according to the rabbit sequence (12) as described previously (11). The sense and antisense primers used for PCR, the size of PCR products, and PCR cycles in each labeled cDNA probe were as follows: CETP: sense, 5'-CTTCCATAAACTGCTCCTG-3'; antisense, 5'-CCTGGGTC-TCGCACTTTCT-3'; size, 482 base pairs, 30 cycles; glyceraldehyde-3-phosphate dehydrogenase: sense, 5'-ATGGTCTACATGTTCCAGTA-3'; antisense, 5'-TAAGCAGTTGGTGGTGCAGG-3'; size, 343 base pairs, 30 cycles. To make the cDNA probe for LDL-receptor (LDL-R), reverse transcription-PCR was done according to the rabbit sequence (13) using the following primers: sense, 5'-TGCATCCATGGCAGCCGGCAGTGT-3'; antisense, 5'-AGGCGGCGGCTCAGGCCACGTCGT-3'; size, 1822 base pairs; 35 cycles. The probe was cloned into pGem3zf(3) *Sma*I site. The labeled cRNA probe for LDL-R were produced using ECL random prime labeling system (Amersham, Japan). Poly(A⁺) RNA was isolated from total RNA with Oligotex Super (Rosche, Japan), and the abundance of each mRNA was determined by Northern blotting.

Measurement of CETP Mass—Rabbit CETP mass was measured as

follows.² Briefly, rabbit CETP was purified from rabbit plasma according to the purification method of human CETP described by Kato *et al.* (14). Rabbit CETP was emulsified in equal volumes of Freund's complete adjuvant and was injected into the foot pads of Balb/c mice. After the first injection of rabbit CETP solution, it was injected 4 times every 5 days. Popliteal lymph node cells of the mice were obtained 2 days after the final injection. Then, the cells were fused with mouse myeloma cells using polyethylene glycol 4000. Media conditioned by the resulting hybridomas were screened for CETP inhibition as described previously (11). Two monoclonal antibodies to neutralize the activity to rabbit CETP, JRC1 and JRC2, were obtained and used in the enzyme-linked immunosorbent assay system. JRC1 was used as the capture monoclonal antibodies, and biotinylated JRC2 was used as the detection monoclonal antibodies. A CETP preparation isolated from rabbit plasma with a JRC1-Sepharose affinity column was used as a standard of the enzyme-linked immunosorbent assay system. The detection limit of the assay was approximately 10 ng of CETP/ml (1 ng/well).

Macroscopic Examination and Measurement of Cholesterol in the Aorta—The aorta was opened longitudinally along the mid-thoracic line, and the surface area containing lesions were measured without staining by planimetry from the enlarged color photograph as described previously (15). The aorta was then cut into pieces (2 × 2 mm) and was delipidated with a chloroform/methanol solution (2:1 v/v). The aortic cholesterol content was measured as described previously (16) and was expressed as mg/g wet weight of aorta.

Biochemical Analysis—The plasma cholesterol concentrations were measured in whole plasma and in the HDL-containing supernatant after the precipitation of VLDL + LDL with dextran Mg²⁺ using the Wako total cholesterol and HDL cholesterol measuring kit (Wako Ltd., Japan). Concerned with the plasma taken at the end of the study when all rabbits were sacrificed, HDL were isolated from the plasma by ultracentrifugation and fractionated by size using a 1.6 × 50-cm Suprose 6B HPLC column as described previously (17), and the HDL cholesterol concentrations were measured. The plasma constituents related to liver function were analyzed using an automatic analyzer (Hitachi Ltd., Japan).

Statistical Analysis—All values are presented as the mean ± S.E. of the mean. Comparisons among three or more groups were made using one-way analysis of variance (ANOVA) followed by Dunnett's modified *t* test. Differences were considered to be statistically significant at a value of $p < 0.05$.

RESULTS

In the rabbits injected with antisense ODNs, the total cholesterol concentrations and the CETP mass were all signifi-

² H. Okamoto, M. Kamada, and A. Mizushima, manuscript in preparation.

cantly decreased in 12 and 16 weeks compared with those injected with sense ODNs and the control animals (Fig. 1). The HDL cholesterol concentrations measured by the precipitation assay did not significantly change among the groups fed a cholesterol diet until 12 weeks (Fig. 1). However, the HDL cholesterol concentrations, measured after the isolation by ultracentrifugation and HPLC, were significantly increased at 16 weeks in the rabbits injected with antisense ODNs compared with those injected with sense ODNs and the control animals (21.57 ± 1.70 mg/dl versus 15.95 ± 1.36 mg/dl, 16.35 mg/dl \pm 2.10) (Fig. 1). Triglyceride concentrations did not significantly change in the four groups (Fig. 1). Fig. 2 shows a typical example of Northern blot analyses of hepatic mRNAs in each group. When the amount of hepatic CETP mRNA and LDL-R mRNA were measured by scanning and expressed as a ratio to glyceraldehyde-3-phosphate dehydrogenase mRNA, the values were (0.87 ± 0.07 , 0.33 ± 0.05) in the control group, (0.85 ± 0.06 , 0.41 ± 0.03) in the sense group, (0.68 ± 0.04 , 0.63 ± 0.06) in the antisense group, and (0.63 ± 0.06 , 0.66 ± 0.06) in the standard group, respectively. A significant reduction of CETP mRNA and a significant increase of LDL-R mRNA were observed in the animals injected with antisense ODNs compared with those injected with the sense ODNs and the control animals. Aortic cholesterol contents and the aortic percentage lesion to total surface area were significantly lower in the animals injected with antisense ODNs than in the animals injected with sense ODNs and in the control animals (Fig. 3). We measured the plasma constituents related to liver function (glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, γ -GTP, alkaliphosphatase, and total bilirubin; data not shown). These levels did not significantly differ among the animals fed a cholesterol diet.

DISCUSSION

In the present study, an injection of ASOR-poly(L-lysine) antisense ODNs complex reduced the hepatic CETP mRNA, plasma CETP activities, and the plasma total cholesterol. As a result, it suppressed atherosclerosis, whereas it did not affect

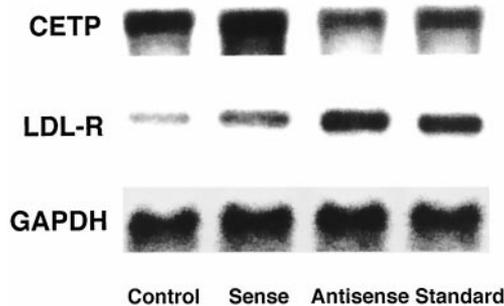
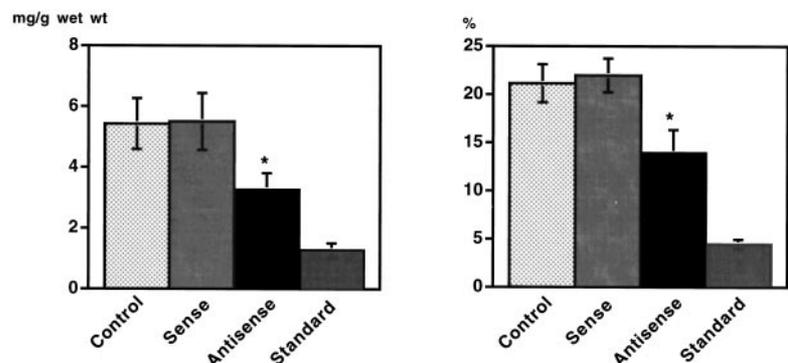


FIG. 2. The typical example of the Northern blot analyses of hepatic CETP, LDL-R, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA in the four groups.

FIG. 3. Aortic cholesterol contents (left panel) and the aortic percentage lesion to total surface area (right panel). Control, the rabbits fed only a 0.3% cholesterol diet; Sense, the rabbits fed a 0.3% cholesterol diet and injected with sense ODNs; Antisense, the rabbits fed a 0.3% cholesterol diet and injected with antisense ODNs; Standard, the rabbits fed a standard diet. Values are the mean \pm S.E. *, $p < 0.05$.



HDL cholesterol and triglyceride concentrations. Although we used the oligodeoxynucleotides of phosphodiester, our antisense injection was considered to be successful for the following reasons. (a) The asialoglycoprotein-poly(L-lysine) antisense complex is rapidly and preferentially taken up by the liver (18, 19) and has enhanced resistance to nuclease degradation in plasma (20). Within 10–20 min of the intravenous administration of ASOR-poly(L-lysine) DNA complex, 80–85% of the total amount was found within the liver, 80% of which was localized specifically to hepatocytes (18, 19). In the above time frame for intravenous delivery, the vast majority of the oligodeoxynucleotides of phosphodiester bound to asialoglycoprotein-poly(L-lysine) conjugate remained intact (20). In the rabbits fed a cholesterol diet, increased plasma CETP mass could be explained by the effects on CETP synthesis, which was consistent with the observed effects of cholesterol on liver mRNA (21, 22). CETP activities contribute to elevated cholesterol concentrations in the patients with hypercholesterolemia and those with combined hyperlipidemia, although they do not constitute final proof (23). In humans with CETP deficiency, LDL catabolic rate is enhanced (24), and down-regulation for the LDL receptor in transgenic mice containing human CETP has been also observed (25). In our study, it was shown that plasma CETP was reduced possibly by suppression of the production of CETP by an antisense ODNs against CETP and that suppression of the increased LDL-R mRNA in the liver might also contribute to the reduction of the total cholesterol concentrations. Plasma CETP concentration showed a positive correlation with LDL cholesterol concentration and molecular weight in cynomolgus monkey when CETP levels and LDL cholesterol concentration were in wide ranges (26). In our study, however, HDL cholesterol concentrations did not significantly change at 12 weeks in spite of the reduction of CETP. We previously showed that the total cholesterol concentrations and the CETP activities were all significantly decreased for 96 h, whereas the HDL cholesterol concentrations returned to the base line at 96 h, when ASOR-poly(L-lysine) antisense ODNs against CETP was injected (11). Blood samples were drawn 4 days (96 h) after the injection of ODNs in the present study, which may partly explain why HDL cholesterol levels were not significantly changed. However, the main reason why HDL cholesterol levels were not significantly changed was possibly due to the method used. Unfortunately, we used the precipitation assay using Dextran Mg^{2+} to measure HDL cholesterol, which may be inaccurate when VLDL + LDL cholesterol are much increased as in our study. In fact, in the rabbits injected with antisense ODNs, the HDL cholesterol concentrations were significantly increased at 16 weeks compared with those injected with sense ODNs and the control animals, when they were measured after the isolation by ultracentrifugation and a HPLC. In our study, the total cholesterol decreased substantially more than the HDL cholesterol increased. Although the

homozygotes for CETP deficiency, which showed almost no CETP levels, demonstrated markedly elevated HDL-C and plasma apoA-I levels (3, 4), wide-ranged CETP levels showed no significant correlation to HDL cholesterol in healthy Japanese (27) and normotriglyceridemic man (28). In our study, since the CETP is from low to high levels in the four groups, it might be speculated that the reduction of CETP affected HDL cholesterol little. In CETP inhibition in the rabbits fed a standard diet with antibody, the major phenotypic effect is increased HDL levels (29). In the transgenic mice expressing human CETP, CETP monoclonal antibody, TP2 suppressed plasma CETP activity, whereas the liver CETP mRNA was increased (30). In our study, however, the rabbits were fed with a cholesterol diet, and the liver CETP mRNA was suppressed with antisense ODNs against CETP. Further studies are called for to elucidate the exact effect of suppression of CETP in the liver on HDL metabolism in hypercholesterolemia. The exact role of CETP in the development of atherosclerosis has been controversial (4–10, 31, 32). Zhong *et al.* (7) reported that the increased risk of coronary heart disease in Japanese-American men with CETP gene mutation was largely present in individuals with HDL cholesterol 40–60 mg/dl, which was in the normal range and that LDL cholesterol levels in the patients were not different compared with the control men (7). In consideration of the lipoprotein cholesterol profile, these findings are hard for us to explain why atherosclerosis developed in the patients. These findings may suggest the anti-atherogenicity of CETP independent of plasma LDL and/or HDL cholesterol. Although Yamashita *et al.* (33) showed that very high density lipoprotein called pre- β HDL, induced by CETP, had a potent anti-atherogenic function, it should be remembered that pre- β HDL was increased in the hypercholesterolemic patients or in the patients with the disorder of other lipid metabolisms (34). Inazu *et al.* (4) previously showed that the homozygotes for CETP deficiency had increased levels of HDL cholesterol and decreased levels of low density lipoprotein cholesterol and that there was no evidence of premature atherosclerosis in the families with CETP deficiency, which might be associated with an increased life span. In the studies using CETP transgenic mice, the transgenic mice expressing only CETP had significantly more early atherosclerotic lesions in the proximal aorta than controls (9), whereas the transgenic mice expressing both human CETP and apoCIII showed the inhibition of the development of early atherosclerotic lesions (10). CETP was more closely associated with carotid intima media thickness than HDL cholesterol in human (32). In conclusion, in this study we showed for the first time that increased plasma VLDL or/and LDL could be reduced by suppression of CETP, which as a result suppressed atherosclerosis. Although fenofibrate has been reported to reduce plasma CETP activity and normalize the dense LDL profile (35), the development of the new drug that can reduce plasma CETP as a main effect is called for to reduce plasma VLDL or/and LDL cholesterol and to prevent atherosclerosis.

Acknowledgment—We thank Mr. Yoshikazu Watanabe for his expert technical assistance.

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J. Biol. Chem. 1998, 273:5033-5036.
doi: 10.1074/jbc.273.9.5033

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