Effects of Deletion of the Carboxyl-terminal Domain of ApoA-I or of Its Substitution with Helices of ApoA-II on in Vitro and in Vivo Lipoprotein Association*

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In the present study, the lipoprotein association of apoA-I, an apoA-I (ΔAla190–Gln243) deletion mutant and an apoA-I (Asp1–Leu189)/apoA-II (Ser12–Gln77) chimera were compared. At equilibrium, 80% of the 125I-labeled apolipoproteins associated with lipoproteins in rabbit or human plasma but with very different distribution profiles. High density lipoprotein (HDL)2,3-associated fractions were 0.60 for apoA-I, 0.30 for the chimera, and 0.15 for the deletion mutant, and corresponding very high density lipoprotein-associated fractions were 0.20, 0.50, and 0.65. Clearance curves after intravenous bolus injection of 125I-labeled apolipoproteins (3 μg/kg) in normolipemic rabbits could be adequately fitted with a sum of three exponential terms, yielding overall plasma clearance rates of 0.028 ± 0.0012 ml·min⁻¹ for apoA-I (mean ± S.E.; n = 6), 0.10 ± 0.008 ml·min⁻¹ for the chimera (p < 0.001 versus apoA-I) and 0.38 ± 0.022 ml·min⁻¹ for the deletion mutant (p < 0.001 versus apoA-I and versus the chimera). Fractions that were initially cleared with a t₁/₂ of 3 min, most probably representing free apolipoproteins, were 0.02 ± 0.04, 0.50 ± 0.06 (p = 0.02 versus apoA-I), and 0.64 ± 0.07 (p = 0.002 versus apoA-I), respectively. At 20 min after the bolus, the fractions of injected material associated with HDL₂,₃ were 0.55 ± 0.06, 0.25 ± 0.03 (p = 0.001 versus apoA-I), and 0.09 ± 0.01 (p < 0.001 versus apoA-I and versus the chimera), respectively, whereas the fractions associated with very high density lipoprotein were 0.15 ± 0.006, 0.25 ± 0.03 (p = 0.008 versus apoA-I), and 0.27 ± 0.03 (p = 0.003 versus apoA-I), respectively. The ability of the different apolipoproteins to bind to HDL₃ particles and displace apoA-I in vitro were compared. The molar ratios at which 50% of 125I-labeled apoA-I was displaced from the surface of HDL₃ particles were 1:1 for apoA-I, 3:1 for the chimera and 12:1 for the deletion mutant, indicating 3- and 12-fold reductions of the affinities for HDL₃ of the chimera and the deletion mutant, respectively. These data suggest that the carboxyl-terminal pair of helices of apoA-I are involved in the initial rapid binding of apoA-I to the lipid surface of HDL. Although the lipid affinity of apoA-II is higher than that of apoA-I, substitution of the carboxyl-terminal helices of apoA-I with those of apoA-II only partially restores its lipoprotein association. Thus, this substitution may affect cooperative interactions with the middle amphipathic helices of apoA-I that are critical for its specific distribution over the different HDL species.

Low plasma levels of high density lipoproteins (HDL)³ and of their major protein component, apolipoprotein A-I (apoA-I), correlate with an increased risk for coronary heart disease (1), and family and twin studies have suggested that decreased HDL levels are partially hereditary (2–5). In addition, HDL and their apolipoproteins increase the net efflux of cellular unesterified cholesterol (6–8) and remove excess cholesterol from peripheral (nonhepatic) cells (9), which may explain the inverse correlation between risk of coronary heart disease and HDL levels (10).

ApoA-I, the major protein component of HDL, is an important determinant of the concentration of HDL in plasma (11). ApoA-I binds and transports plasma lipids, serves as a cofactor for the enzyme lecithin:cholesterol acyltransferase, and increases cholesterol efflux from peripheral tissues (12–14). In addition, apoA-I is an important ligand in the binding of HDL to cell membranes (15, 16). These characteristics contribute to the ability of HDL to induce reverse cholesterol transport and thus to the protective effect of HDL on cardiovascular disease.

ApoA-I is synthesized as a prepropeptide, which is cotranslationally cleaved to pro-apoA-I, and then cleaved during secretion to form the mature 243-amino acid apoA-I protein (17). The secondary structure of apoA-I contains amphipathic helices composed of hydrophobic and hydrophilic surfaces (18–20). It has been demonstrated that the carboxyl-terminal domain of apoA-I plays an important role in lipid binding and in the interaction with cell membranes (16, 21–25). Analysis of patients with reduced plasma concentration of HDL revealed that accelerated catabolism, possibly due to enzymatic degradation, of apoA-I is the most common cause of low HDL levels (26–29). Schmidt et al. (30) demonstrated that deletion of the carboxyl-terminal domain of apoA-I results in decreased in vivo lipoprotein association, in an altered distribution pattern in HDL, and in an increased clearance rate. Recently, we have demonstrated (25) that deletion of the carboxyl-terminal domain of apoA-I decreases the rate but not the extent of in vitro phospholipid association and that this interaction results in the formation of larger discoidal particles with increased apoA-I/phospholipid ratios.

The present study compares the in vitro and in vivo lipopro-
tein binding properties of wild-type human apoA-I, an apoA-I (ΔAla<sup>190</sup>-Gln<sup>243</sup>) carboxyl-terminal deletion mutant, and an apoA-I (Asp<sup>1</sup>-Leu<sup>189</sup>/apoA-II (Ser<sup>12</sup>-Gln<sup>77</sup>) chimera, in which the carboxyl-terminal pair of helices of apoA-I have been substituted with the pair of helices of apoA-II.

**EXPERIMENTAL PROCEDURES**

Reagents—Oligonucleotides were obtained by custom synthesis (Pharmacia, Brussels, Belgium). DNA sequencing was performed on a Pharmacia ALF DNA sequencer. Chromatography materials were obtained from Pharmacia.

Construction of cDNA for Expression of ApoA-I (Asp<sup>1</sup>-Leu<sup>189</sup>/apoA-II (Ser<sup>12</sup>-Gln<sup>77</sup>)—All DNA manipulations were carried out essentially as described (25). cDNAs for expression of wild-type apoA-I and of apoA-I (ΔAla<sup>190</sup>-Gln<sup>243</sup>) in Escherichia coli were obtained as described previously (25).

The DNA fragment for the Ser<sup>12</sup>-Gln<sup>77</sup> segment of apoA-II was amplified by polymerase chain reaction in an automated DNA thermal cycler (Perkin-Elmer) using the 5′-deoxyoligonucleotide dATGGCGCCTCACTGGG GGTTGGCCAGGCTGTGT and the apoA-II (Ser<sup>12</sup>-Gln<sup>114</sup>) segment, and the 3′-deoxyoligonucleotide dATAGGCCCTCTAGGCTGG CTGGTGCCAGGCTGTGT reversed primer, overlapping the apoA-II (Thr<sup>97</sup>-Gln<sup>77</sup>) segment followed with a TGA stop codon and a Nari site. Thirty cycles were performed, consisting of 1 min of denaturation at 94°C, 2 min of annealing at 52°C, and 1.5 min of extension at 72°C. The polymerase chain reaction product was digested with Nari and ligated in the Nari-treated pMC5-apoA-I transformation vector resulting in the pMC5-apoA-I (Asp<sup>1</sup>-Leu<sup>189</sup>/apoA-II (Ser<sup>12</sup>-Gln<sup>77</sup>) vector for the expression of apoA-I (Asp<sup>1</sup>-Leu<sup>189</sup>/apoA-II (Ser<sup>12</sup>-Gln<sup>77</sup>)) in E. coli. All cDNA constructs were confirmed by DNA sequencing, as described previously (25).

Expression and Purification of Apolipoproteins—Apolipoproteins were expressed in the periplasmic fractions of E. coli WK6 host cells as described (25).

Standard apoA-I was isolated from normal human plasma as described previously (17). The purity of proteins was established by SDS-gel electrophoresis (31) and immunoblotting (32).

Pharmacokinetics—Proteins were iodinated by the Bolton and Hunter method (33). The pharmacokinetic properties of wild-type apoA-I, apoA-I (ΔAla<sup>190</sup>-Gln<sup>243</sup>) and apoA-I (Asp<sup>1</sup>-Leu<sup>189</sup>/apoA-II (Ser<sup>12</sup>-Gln<sup>77</sup>) in New Zealand White rabbits were determined as measurement of the residual radioactivity after bolus injection of 125I-labeled proteins (3 μg/kg) in blood samples that were taken at times 1, 2, 5, 10, 20, 30 min and at 1, 2, 3, 4, 5, 6, 7, 8, 24, 28, and 31 h. The results were plotted semilogarithmically, and the curves were fitted with a sum of three exponential terms C(t) = Ae<sup>-a</sup> + Be<sup>-b</sup> + Ce<sup>-c</sup>, by graphical curve peeling (34). The coefficients A, B, and C were calculated from the intercepts on the ordinate, whereas the exponents α, β, and γ were calculated from the slopes. The following clearance parameters were calculated using standard formulas derived by Gibaldi and Perrier (34): total volume of distribution, V<sub>d</sub>; area under the curve, AUC; and plasma clearance rate, Cl<sub>p</sub> = dose/AUC. Statistical differences between these parameters were calculated using the Student t test.

Density Gradient Ultrafiltration and Gel Filtration Chromatography—Continuous density gradient ultracentrifugation (35) was performed using a table top T-100 ultracentrifuge (Analis, Namur, Belgium) in 5-ml tubes. Four hundred μl of rabbit plasma was analyzed by gel filtration on a Superose 6HR column equilibrated with 20 mM Tris-Cl buffer, pH 8.1, containing 0.15 M NaCl, 1 mM EDTA, and 0.02 mg/ml sodium azide in a fast protein liquid chromatography system (Waters Associates, Milford, MA). The levels of phospholipids and cholesterol were determined using standard enzymatic assays (Biomerieux, Marcy, France, and Boehringer Mannheim, Meylon, France, respectively), and the protein levels were determined according to Bradford (36).

Displacement of Radiolabeled ApoA-I from the Surface of HLD—Human HLD<sub>1a</sub>, containing 240 μg of apoA-I in 200 μl, was incubated with 30 μg of 125I-labeled apoA-I for 1 h at 37°C. Nonbound radiolabeled apoA-I was separated from the HLD<sub>1a</sub> fraction by filtration on a Centricron 300 filter (Amicon, Beverly, MA). Radiolabeled HLD<sub>1a</sub> was diluted 8-fold in 20 mM Tris-Cl buffer, and 50-μl aliquots, containing 0.80 μg of radiolabeled apoA-I, were mixed with 50 μl of solutions that contained 0.24, 0.48, 0.96, 1.92, 3.84, 7.68, or 15.36 μg of apoA-I, deletion mutant, or chimeras. After 1 h of incubation at 37°C, free apolipoproteins were separated from the HLD<sub>1a</sub> by filtration. The HLD<sub>1a</sub>-
Radiolabeled apolipoproteins with specific radioactivities of $3 \times 10^6$ cpm/mg of protein were used within 24 h after radio-labeling and analyzed by SDS-polyacrylamide gel electrophoresis to exclude degradation and self-association (not shown). The association of radiolabeled apolipoproteins with lipoprotein particles was studied following in vitro incubation in rabbit plasma for 60 min. Fractions of added apolipoproteins that were associated with HDL$_{2,3}$ particles were 0.60 $\pm$ 0.05 for apoA-I (mean $\pm$ S.E.; n = 6), 0.32 $\pm$ 0.02 for the chimera (p = 0.007 versus apoA-I), and 0.14 $\pm$ 0.005 for the deletion mutant (p < 0.001 versus apoA-I and versus the chimera). Fractions of added apolipoproteins associated with VHDl particles were 0.20 $\pm$ 0.01 for apoA-I, 0.48 $\pm$ 0.05 for the chimera (p > 0.001 versus apoA-I), and 0.65 $\pm$ 0.06 for the deletion mutant (p < 0.001 versus apoA-I and p = NS versus the chimera). Fractions present as free apolipoproteins in the plasma were 0.20 for all three compounds (data not shown). The density distributions of radiolabeled apolipoproteins associated with lipoprotein particles in human plasma are illustrated in Fig. 5. Fractions that were associated with HDL$_{2,3}$ particles were 0.55 $\pm$ 0.06 for apoA-I, 0.30 $\pm$ 0.04 for the chimera (p = 0.006 versus apoA-I), and 0.15 $\pm$ 0.02 for the deletion mutant (p < 0.001 versus apoA-I, p = 0.007 versus the chimera). Fractions that were associated with VHDl particles were 0.25 $\pm$ 0.02 for apoA-I, 0.50 $\pm$ 0.06 for the chimera (p < 0.003 versus apoA-I), and 0.65 $\pm$ 0.05 for the deletion mutant (p < 0.001 versus apoA-I and p = NS versus the chimera). Fractions that were present as free apolipoproteins in the plasma again were 0.20 for all three compounds.

The plasma clearance of radiolabeled wild-type apoA-I, apoA-I ($\Delta$Ala$^{190}$-Gln$^{243}$), and apoA-I (Asp$^{1}$-Leu$^{189}$)/apoA-II (Ser$^{12}$-Gln$^{77}$) was analyzed in rabbits (Fig. 6). The disappearance rates of all proteins could be described by a sum of three exponential terms by graphical curve peeling. The calculated
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Fig. 5. Density distribution of 125I-labeled apolipoproteins in human plasma. Radiolabeled apolipoproteins were incubated for 60 min at 37°C. Continuous gradient ultracentrifugation was performed, and radioactivity in different lipoprotein fractions was measured for apoA-I (●), apoA-I (ΔAla190–Gln243) (△), and apoA-I (Asp1–Leu108)/apoA-II (Ser12–Gln77) (■). The density fractions corresponding to high density lipoproteins HDL2 (d = 1.063–1.125 g/ml), high density lipoproteins HDL3 (d = 1.125–1.210 g/ml), and very high density lipoproteins VHDL (d = 1.21–1.25 g/ml) are indicated. Data represent mean values of six independent experiments.

Fig. 6. In vivo catabolism of 125I-labeled apoA-I (●), apoA-I (ΔAla190–Gln243) (△), and apoA-I (Asp1–Leu108)/apoA-II (Ser12–Gln77) (■) after bolus injection in New Zealand White rabbits. Data represent mean values of six independent experiments.

pharmacokinetic parameters are summarized in Table I. The plasma clearance rate was 0.028 ± 0.0012 ml·min⁻¹ for 125I-labeled apoA-I as compared with 0.025 ± 0.0011 ml·min⁻¹ for apoA-I antigen, as determined in an enzyme-linked immunosorbent assay based on monoclonal antibodies specific for apoA-I following injection of human apoA-I. These data suggest that clearance of apoA-I was not affected by the labeling procedures. Plasma clearance rates of the chimera and of the deletion mutant, respectively, were 3.6-fold and 13.6-fold higher than that of apoA-I (Table I). Values of t₁/₂α, t₁/₂β, and t₁/₂γ were, however, very similar for all apolipoproteins: 3, 220, and 2,300 min, respectively, suggesting that the differences in clearance resulted from differences in the lipoprotein profiles. This is illustrated in Fig. 7, which shows the distributions of cholesterol and phospholipids (upper panel) and of radiolabeled apolipoproteins (lower panel) in the different lipoprotein fractions at 20 min postinjection. Ninety percent of 125I-labeled apoA-I was associated with HDL₂ and HDL₃ particles (fractions 15–25), whereas only 10% was associated with smaller, phospholipid-rich VHDL particles (fractions 26–35). Corresponding values were 60 and 40% for the chimera and 30 and 70% for the deletion mutant.

The lipoprotein binding properties of the three apolipoproteins were further investigated by analyzing the density distribution of radiolabeled apolipoproteins. The distribution patterns at 20 min postinjection are illustrated in Fig. 8. At 20 min postinjection, HDL₂ and HDL₃-associated fractions were 0.55 ± 0.06 for apoA-I, 0.25 ± 0.03 for the chimera (p = 0.001 versus apoA-I) and 0.09 ± 0.01 for the deletion mutant (p < 0.001 versus apoA-I and versus the chimera) (Fig. 9). At 4h postinjection, HDL₂ and HDL₃-associated fractions were 0.43 ± 0.04, 0.19 ± 0.02 (p < 0.001 versus apoA-I) and 0.08 ± 0.006 (p < 0.001 versus apoA-I and versus the chimera), respectively (Fig. 9). At 24h postinjection, HDL₂ and HDL₃-associated fractions were 0.34 ± 0.05, 0.14 ± 0.02 (p = 0.004 versus apoA-I), and 0.06 ± 0.008 (p < 0.001 versus apoA-I and p = 0.004 versus the chimera), respectively (Fig. 9). Estimated half-lives of HDL₂ and HDL₃-associated protein were 2,200 ± 130 min for apoA-I, 2,500 ± 300 min (p not significant) for the chimera and 2,400 ± 240 min (p not significant) for the deletion mutant, which are very similar to the values of t₁/₂γ. At 20 min postinjection, VHDL-associated fractions were 0.15 ± 0.006, 0.25 ± 0.03 (p = 0.008 versus apoA-I) and 0.27 ± 0.03 (p = 0.003 versus apoA-I, and p not significant versus the chimera), respectively (Fig. 9). At 4h postinjection, corresponding fractions were 0.05 ± 0.005, 0.08 ± 0.01 (p = 0.002 versus apoA-I), and 0.10 ± 0.012 (p = 0.003 versus apoA-I and p not significant versus the chimera) (Fig. 9). At 24h postinjection, fractions were 0.02 ± 0.002, 0.04 ± 0.007 (p = 0.02 versus apoA-I), and 0.04 ± 0.008 (p = 0.04 versus apoA-I and p not significant versus the chimera) (Fig. 9). Estimated half-lives of VHDL-associated proteins were 260 ± 45 min for apoA-I, 240 ± 35 min (p not significant) for the chimera, and 280 ± 25 min (p not significant) for the deletion mutant, which are very similar to the values of t₁/₂γ. Fractions that were not associated with lipoproteins at 20 min postinjection and that most probably were cleared as free apolipoproteins were 0.30 ± 0.04 for apoA-I, 0.50 ± 0.06 (p = 0.02 versus apoA-I) for the chimera, and 0.64 ± 0.07 (p = 0.002 versus apoA-I and p not significant versus the chimera) for the deletion mutant.

Incubation of 50–μl aliquots of radiolabeled HDL₃ containing 0.8 μg of radiolabeled apoA-I, with 50–μl aliquots containing increasing amounts (0.24, 0.48, 0.96, 1.92, 3.84, 7.68, or 15.36 μg) of apoA-I, the chimera, or the deletion mutant resulted in a concentration-dependent displacement of radiolabeled apoA-I from the surface of HDL. Fifty percent displacement was obtained with 0.9 μg of apoA-I, 3.0 μg of the chimera, and 8.7 μg of the deletion mutant, thus at 1:1, 3:1, and 12:1 molar ratios of added protein to HDL₃-associated 125I-labeled apoA-I, respectively (Fig. 10). These data indicate that the affinity for HDL₃ of 125I-labeled apoA-I was identical to that of nonlabeled apoA-I, whereas the affinities of, respectively, the chimera and the deletion mutant were 3- and 12-fold lower.

DISCUSSION

The variability in HDL cholesterol levels is largely determined by differences in the fractional catabolic rate of apoA-I, which is inversely correlated with HDL particle size (39). In order to analyze the role of the carboxyl-terminal domain of apoA-I in phospholipid binding, lipoprotein association, HDL particle size distribution, and clearance, mutants of apoA-I have been generated. In the present study, the in vitro and in vivo lipoprotein binding properties of apoA-I, an apoA-I (ΔAla190–Gln243) deletion mutant, and an apoA-I (Asp1–Leu108)/apoA-II (Ser12–Gln77) chimera were compared. In the apoA-I (Asp1–Leu108)/apoA-II (Ser12–Gln77) chimera, the Ala190–Gln243 carboxyl-terminal domain of apoA-I was substituted with the Ser12–Lys28 and Pro232–Val246 helical segments of apoA-II. Previously, it has been shown that synthetic peptides overlapping with these apoA-II sequences associated with phospholipids, suggesting that these helical segments consti-
tute phospholipid binding domains (40, 41). Furthermore, epitope-mapping studies showed that antibodies to the carboxy-terminal domain of apoA-I bound to an epitope in the Gln36–Gln77 segment of apoA-II, demonstrating significant structural homology between these domains (42). Finally, apoA-II can displace apoA-I from the surface of recombinant HDL particles without loss of phospholipids or major change in particle size (43).

125I-Labeled apoA-I associated preferentially (60%) with HDL2 and HDL3 particles both in rabbit and human plasma. Deletion of the Ala190–Gln243 carboxy-terminal domain of apoA-I did not reduce the extent (80%) of in vitro lipoprotein association in rabbit and human plasma under equilibrium conditions but altered its distribution profile. Only 15% of the apoA-I (Ala190–Gln243) deletion mutant associated with HDL2,3 particles. Although the predicted secondary structure and the amphipathicity of the chimera were very similar to those of apoA-I, only 30% of the chimera associated with HDL2,3 particles. Because lipoprotein distribution profiles in human and rabbit plasma were very similar, rabbits were used as model animals to investigate the effects of changed lipoprotein distribution of both the chimera and the deletion mutant on their pharmacokinetic properties.

Following bolus injection of 125I-labeled apoA-I in rabbits, it was cleared with a rate of 0.028 ml min⁻¹. This value is very similar to that determined by Ikewaki et al. (39) following bolus injection of either exogenously or endogenously labeled apoA-I in humans. Deletion of the carboxy-terminal domain of apoA-I resulted in a 13.6-fold increased clearance rate. This was most probably due to an enhanced clearance in the α-phase (64%) as compared with 30% for apoA-I of free apolipoprotein in solu-

| Parameter          | ApoA-I     | ApoA-I (Asp1–Leu189)/apoA-II (Ser12–Gln77) | ApoA-I (ΔAla190–Gln243) |
|--------------------|------------|------------------------------------------|-------------------------|
| Vₕ (ml)            | 170 ± 10   | 160 ± 6.1                                | 180 ± 8.2               |
| AUC (μg · min · ml⁻¹) | 360 ± 13   | 86 ± 4.9*                                | 26 ± 2.5*               |
| Clp (ml · min⁻¹)   | 0.028 ± 0.0012 | 0.10 ± 0.008*              | 0.38 ± 0.022*           |

* p < 0.001.
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Fig. 10. Displacement of 125I-labeled apoA-I from the surface of HDL₃ with increasing amounts of apoA-I (○), apoA-I (ΔAla180, Gln243) (△), and apoA-I (Asp1–Leu189)/apoA-II (Ser12–Gln77) (■).
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