Use of Antibody Specificity to Study the Surface Disposition of Apoprotein A-I on Human High Density Lipoproteins*

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Only ~10% of the apoprotein A-I (apo-A-I) in intact high density lipoprotein 2 (HDL₂) is detected by radioimmunoassay, suggesting that not all of HDL₂-apo-A-I is immunologically reactive. Previous work had indicated that the COOH-terminal region of HDL₂-apo-A-I was immunologically more reactive than the NH₂ region, whereas the two terminal regions of the isolated apo-A-I molecule were equally reactive. To confirm these immunologic differences, apo-A-I and HDL₂ were used as immunogens and the specificities of antisera were compared. In addition, an anti-apo-A-I antiserum was absorbed with HDL₂ and the binding capacity of the absorbed antiserum for the COOH- and NH₂-terminal fragments of apo-A-I was ascertained.

HDL₂ was isolated by ultracentrifugation (d 1.083 to 1.214) and apo-A-I was obtained from delipidated HDL₂ by column chromatography (Sephadex G-200, 0.01 M Tris, pH 8.6, 8 M urea). CNBr fragments were prepared corresponding to the COOH- and NH₂-terminal regions (CNBr I and CNBr II, respectively). Apo-A-I and the fragments were iodinated with Na¹²³I using lactoperoxidase. The maximal binding of these purified ¹²³I-labeled proteins by the antiserum was assessed in double antibody radioimmunoassays.

Anti-apo-A-I antiserum bound ~90% of ¹²⁵I-apo-A-I (~100 pmol) and ~60% of ¹²⁵I-COOH-terminal (~150 pmol) and ¹²⁵I-NH₂-terminal fragments (~80 pmol). Anti-HDL₂ antisera bound similar amounts of ¹²⁵I-apo-A-I and ¹²⁵I-COOH-terminal fragment but they bound only ~10% of the ¹²⁵I-NH₂-terminal fragment (~12 pmol). Antiserum produced against the isolated purified fragments bind only the appropriate ¹²⁵I-labeled fragments and ~60% of ¹²⁵I-apo-A-I. Thus, apo-A-I stimulated the production of antisera which contained antibodies directed against both ends of the molecule; HDL₂-apo-A-I by contrast stimulated antiserum directed preferentially to the terminal region of the molecule.

In the antiserum absorption experiments, when increasing amounts of HDL₂ protein (27 to 1500 µg/ml of antisemum) were added to the anti-apo-A-I antiserum, the capacity of the antiserum to bind both ¹²⁵I COOH and ¹²⁵I NH₂-terminal fragments diminished. However, after addition of limiting amounts of HDL₂ there was a greater depletion of the binding capacity of the antiserum for the ¹²⁵I-COOH-terminal than for the ¹²⁵I-NH₂-terminal peptide. When saturating amounts of HDL₂ were added, only 5% of the original binding capacity for the ¹²⁵I-COOH-terminal remained, whereas 25% of the ¹²⁵I-NH₂-terminal was still bound. These results support previous findings and are compatible with a more "exposed" position for the COOH-terminal of apo-A-I on the surface of intact HDL₂. All workers agree that the protein moieties of lipoproteins (apolipoproteins) are located on or near the surfaces of the spherical lipoprotein particles (1-4). However, not all of the regions of all of the apolipoproteins are equally exposed on the surfaces of HDL. The best evidence for this comes from immunologic studies. For example, when the apo-A-I contents of intact HDL₂ are quantified by radioimmunoassay, ~10% of the expected amounts are detected (5, 6). By contrast, nearly all of the apo-A-II in intact HDL₂ is detectable by radioimmunoassay (7, 8). This suggests that whereas all of the antigenic sites of apo-A-II are immunologically reactive, only a minority of the sites of apo-A-I are reactive on the surface of intact HDL₂. Indeed, HDL₂ competes more effectively with the ¹²⁵I-labeled COOH-terminal fragment of apo-A-I than it does with the ¹²⁵I-labeled NH₂-terminal fragment for limited amounts of anti-apo-A-I antisera (9). The greater immunoreactivity of the COOH-terminal region is compatible with several interpretations including the one we favor; namely, that the COOH-terminal portion of apo-A-I is more "exposed" on the surface of HDL₂.

The aim of the present experiments was to confirm the relatively greater immunologic activity of the COOH-terminal region of apo-A-I in intact HDL₂ (HDL₂-apo-A-I) by two different methods. (a) Antisera reflect the specificities of immunizing antigens (10), therefore if the COOH-terminal region of HDL₂-apo-A-I is indeed the more reactive terminus, HDL₂ ought to stimulate the production of antisera which contain predominantly anti-COOH-terminal antibodies, whereas isolated apo-A-I should provoke the production of antibodies directed against both ends of the molecule (9). To test this hypothesis, antisera were produced against HDL₂.

The abbreviations used are: HDL₂, high density lipoprotein; apo-A-I, apoprotein A-I from HDL₂; apo-A-II, apoprotein A-II from HDL₂; LDL₂, low density lipoprotein; VLDL₂, very low density lipoprotein.
and the specificities of the antisera were compared to those of antisera produced against isolated apo-A-I. (b) If the COOH-terminal of the apo-A-I in HDL₂ is the more "exposed" terminal, the addition of HDL₂ to anti-apo-A-I antisera should result in the preferential absorption of anti-COOH-terminal antibodies (compared with anti-NH₂-terminal antibodies) from the anti-apo-A-I antisera. To test the second hypothesis, increasing amounts of HDL₂ were added to an anti-apo-A-I antiserum which was able to bind both the ¹²⁵I-COOH- and ¹²⁵I-NH₂-terminal fragments of apo-A-I, and the binding capacity of the antiserum for the two fragments was tested during the course of its absorption with HDL₂. The results of both experimental approaches are compatible with a relatively more "exposed" position for the apo-A-I COOH-terminal region on the surface of HDL₂.

METHODS

HDL₂ was isolated as described (5) from the plasmas of healthy young donors by ultracentrifugation at d 1.085 to 1.124. These preparations yielded immunoprecipitin lines (11) against human anti-apo-A-I, anti-apo-A-II, and anti-apo-C but not against anti-apo-B or anti-human serum albumin antisera (Behring Diagnostics, Inc., Sommerville, N. J.). To isolate the apoproteins of HDL₂ (d 1.090 to 1.19) by column chromatography, HDL₂ was delipidated with ether/ethanol solutions (12) and the proteins were solubilized in 0.05 M Tris, pH 6, 8 M urea, and filtered on a column (2.5 × 90 cm) of Sephadex G-200 equilibrated with Tris/urea (13). The resulting peak regions were pooled and dialyzed against 0.16 M NaCl, 1 mM EDTA, pH 8.0. Apo-A-I was purified by rechromatography on the same column. CNBr fragments of apo-A-I were prepared according to Baker et al. (14) as previously described (9). Apoproteins and CNBr fragments were identified by disc gel polyacrylamide electrophoresis in urea (15) and sodium dodecyl sulfate (16) and by amino acid analysis. Protein contents were quantified by the method of Lowry et al. (17) using bovine serum albumin standards (Sigma Chemical Co., St. Louis, Mo.) or amino acid analysis.

Antisera against HDL₂, apo-A-I, and the isolated terminal fragments of apo-A-I were produced in rabbits using Freund’s complete adjuvant (5). Each rabbit was bled two to four times, each time 8 to 12 days after a "booster" injection of antigen. Absorption of antiserum with HDL₂ was carried out as follows: 27 to 1500 µg of HDL₂ protein were added to an constant volume per ml of antiserum to a series of test tubes. The HDL₂/antiserum mixtures were incubated at 37°C for 1 h and then at 4°C for 18 h. Test tubes were centrifuged at 4°C for 45,000 × g min. The clear supernatants were carefully aspirated and were used in ¹²⁵I-COOH- and ¹²⁵I-NH₂-terminal fragment binding assays.

The procedures for the isolation of apo-A-I and of the CNBr I and CNBr II fractions of apo-A-I (the COOH- and NH₂-terminal regions, respectively) have been published previously (9). Specific radioactivities of these proteins varied between 2 and 8 × 10⁶ cpm/ µg. Radioimmunoadsorbent tubes contained ¹²⁵I-labeled HDL₂, ¹²⁵I-apo-A-I, or ¹²⁵I-COOH-terminal or ¹²⁵I-NH₂-terminal fragments (50 µl, about 15,000 cpm/µl), antiserum (100 µl, diluted 1:200), 0.05 M barbital buffer, pH 8.6, in sufficient amounts to bring the volume to 500 µl. For ¹²⁵I-HDL₂, ¹²⁵I-apo-A-I, and ¹²⁵I-NH₂-terminal assays the barbital buffer contained 3% albumin; for the ¹²⁵I-COOH-terminal assays, it contained 0.01% Triton X-100. After 42 h of incubation at 4°C, 50 µl of goat anti-rabbit IgG were added and incubation was continued for another 16 h. Tubes were also included from which anti-apo-A-I, anti-apo-A-I fragment, or anti-HDL₂ antisera were omitted. Radioactivity was counted in a Packard Auto-Gamma spectrometer.

Precipitation in the absence of specific antisera did not exceed 5% of added counts and was subtracted from all tubes for calculation of results. B₀ = specific precipitation (in counts per min) in the absence of sample; B = specific precipitation in the presence of sample; T = total counts per min added per tube. Results of binding experiments are also expressed in mass units. These calculations are based on counts per min precipitated = specific radioactivity of the protein in the precipitate.

RESULTS

The specificities of antisera produced against HDL₂, apo-A-I, and the COOH- and NH₂-terminal fragments of apo-A-I are given in Table I.

### Table I

<table>
<thead>
<tr>
<th>Antiserum</th>
<th>¹²⁵I-antigen bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-apo-A-I</td>
<td></td>
</tr>
<tr>
<td>R 130-1, -2, -3</td>
<td>88-91</td>
</tr>
<tr>
<td>R 131-1, -2, -3, -4</td>
<td>92-91</td>
</tr>
<tr>
<td>Anti-HDL₂</td>
<td></td>
</tr>
<tr>
<td>R 173-1, -2, -3, -4</td>
<td>51-60</td>
</tr>
<tr>
<td>R 173-1, -2, -3</td>
<td>71-84</td>
</tr>
<tr>
<td>Anti-COOH-terminal</td>
<td></td>
</tr>
<tr>
<td>R 151-1, -2</td>
<td>18-52</td>
</tr>
<tr>
<td>R 157-1, -2, -3</td>
<td>44-51</td>
</tr>
<tr>
<td>Anti-NH₂-terminal</td>
<td></td>
</tr>
<tr>
<td>R 152-1, -2, -3, -4</td>
<td>23-55</td>
</tr>
<tr>
<td>R 158-3</td>
<td>28-42</td>
</tr>
</tbody>
</table>

![Fig. 1](http://example.com/f1.png)

**Fig. 1.** Binding of ¹²⁵I-apo-A-I and ¹²⁵I-COOH-terminal (CNBr I) and ¹²⁵I-NH₂-terminal (CNBr II) regions of apo-A-I by anti-apo-A-I and anti-HDL₂ antisera. Double antibody radioimmunoadsorbent tubes were set up which contained the indicated dilutions of antisera and ¹²⁵I-labeled proteins. Nonisotopic proteins were omitted. Anti-apo-A-I antisera (top panel) bound up to ~90% of ¹²⁵I-apo-A-I (B₀/T = ~0.9) and ~60% of each of the ¹²⁵I-labeled fragments. Antiseras (bottom panel) bound similar amounts of ¹²⁵I-apo-A-I and ¹²⁵I-COOH-terminal fragments, but binding of ¹²⁵I-NH₂-terminal portions was <10%. The different specificities of anti-apo-A-I and anti-HDL₂ reflect the different structural conformations of apo-A-I and HDL₂-apo-A-I.

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[55x660]antibodies (compared with anti NH₂-terminal antibodies) result in the preferential absorption of anti-COOH-terminal antibodies (compared with anti NH₂-terminal antibodies) from the anti-apo-A-I antisera. To test the second hypothesis, increasing amounts of HDL₂, to anti-apo-A-I antisera should
Antisera directed against HDL bound both apo-A-I and apo-A-II and small amounts of VLDL and LDL. It is thought that the cross-reactivity with VLDL probably represents immunologic reaction with the apo-C proteins found both in HDL and VLDL (18-20). With respect to LDL, others, too, have found it difficult to obtain anti-HDL antisera entirely free of anti-LDL activity even when HDL preparations apparently free of LDL were used as antigens (21). Perhaps the HDL preparations used in these studies carried trace amounts of LDL. More likely, they may have been contaminated by small amounts of Lp(a) (22). However, the ability of some of the anti-HDL antiserum to bind small amounts of VLDL and LDL does not influence these experiments because we detected interactions only between labeled moieties and the specific antibody populations directed against them. Other antibody populations remained undetected and thus are irrelevant so long as the labeled antigen used in the experiments are pure as ours appeared to be (5, 9).

The anti-apo-A-I and the anti-apo-A-II fragment antisera were able to bind 125I-labeled apo-A-I and HDL, but not 125I-labeled apo-A-II, VLDL, or LDL. The anti-COOH terminus antisera did not bind the NH2-terminal peptide and vice versa. Thus, the antisera possessed the requisite specificities. Note that HDL was bound by both the anti-COOH- and the anti-NH2-terminal antisera, suggesting that both termini of apo-A-I in intact HDL (HDL2-apo-A-I) are expressed on the surface of HDL. The experiments reported on below ask "Is one of the termini more reactive than the other?"

Each antiserum bound 125I-apo-A-I (Fig. 1 and Table II). All results represent maximum precipitation of the 125I-labeled moieties (B ∗ × 100%) by the indicated antiserum (see Fig. 1). The same results, in picomoles, are given in parentheses. Note that the 125I-COOH-terminal and 125I-NH2-terminal portions of apo-A-I were precipitated to varying extents by the different antiserum. COOH/NH2 ratios are ratios of the per cent precipitabilities of the two apo-A-I fragments. For specificities of antisera see Table I. Each label was tested two to four times against each antiserum, all values are encompassed by the ranges given.

### TABLE II

<table>
<thead>
<tr>
<th>Antiserum</th>
<th>125I-labeled protein</th>
<th>COOH/NH2 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-apo-A-I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R 130-1, -2, -3</td>
<td>41-65 (117-186)</td>
<td>26-63 (42-102)</td>
</tr>
<tr>
<td>R 131-1, -2, -3, -4</td>
<td>19-38 (54-109)</td>
<td>25-48 (40-77)</td>
</tr>
<tr>
<td>Anti-HDL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R 172-1, -2, -3, -4</td>
<td>45-66 (129-189)</td>
<td>5-11 (8-18)</td>
</tr>
<tr>
<td>R 173-1, -2, -3, -4</td>
<td>46-68 (131-195)</td>
<td>6-10 (10-16)</td>
</tr>
<tr>
<td>Anti-COOH-terminal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R 157-1, -2, -3, -4</td>
<td>35-70 (100-217)</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Anti-NH2-terminal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R 152-1, -2, -3, -4</td>
<td>&lt;2</td>
<td>17-25 (27-40)</td>
</tr>
</tbody>
</table>

**Fig. 2.** Absorption by HDL of the binding capacity of anti-apo-A-I antiserum for the 125I-COOH- and 125I-NH2-terminal fragments of apo-A-I. The indicated amounts of HDL protein were added to antiserum R 130-3 (abscissa). Following incubation (1 h at 37° and 18 h at 4°) and centrifugal separation of HDL-antibody complexes (45,000 × g min at 4°), the capacity of antibody supernatants to bind the 125I-COOH- and 125I-NH2-terminal fragments was assessed in a double antibody assay system. Maximal binding was achieved with dilutions of antisera between 1:100 and 1:500. Results are given as picomoles of 125I-NH2- or COOH-terminal fragment precipitated. Calculations are based on the known specific radioactivities of the labeled fragments.

**Fig. 3.** Competitive binding of 125I-apo-A-I versus nonisotopic apo-A-I, or versus nonisotopic NH2-terminal fragment of apo-A-I. Anti-apo-A-I antiserum R 130-3, unabsorbed and absorbed with 1000 μg of HDL2 protein/ml of antiserum, was used with 125I-apo-A-I as tracer. As increasing amounts of unlabeled apo-A-I or NH2-terminal fragment were added (abscissa) to the assay, both apo-A-I and the NH2 fragment inhibited the binding of labeled apo-A-I. In the assay containing unabsorbed antiserum, ~300 times as much NH2-terminal fragment as apo-A-I was required to produce similar degrees of inhibition, whereas in the assay containing absorbed R 130-3, only ~15 times as much NH2 fragment as apo-A-I was required. Thus, in the assay with absorbed R 130-3, the NH2-terminal fragment was ~20 times more effective as a competitor versus 125I-apo-A-I than it was in the assay containing the unabsorbed antiserum.
antisera (except the anti-NH$_2$ fragment antisera) bound the $^{125}$I-labeled COOH-terminal fragment. Similarly, all of the antisera (except for the anti-COOH-terminal antisera) bound the $^{125}$I-labeled NH$_2$-terminal fragment. However, the relative maximum binding of the two terminal fragments differed greatly. The COOH and NH$_2$ fragments were bound to about the same extent by the anti-apo-A-I antisera, i.e., the COOH/NH$_2$ ratios varied between 0.7 and 2.0. By contrast, the anti-HDL$_2$ antisera bound the COOH-fragments preferentially; the COOH/NH$_2$ ratios varied between 5.0 and 10.6. The anti-fragment sera bound only the appropriate fragments. (The COOH/NH$_2$ ratio for anti-COOH-terminal antisera exceeds 0 whereas the ratio for anti-NH$_2$-terminal antisera was less than 0.05).

The results of the antibody absorption experiments are given in Fig. 1. The unabsorbed R 130-3 anti-apo-A-I antiserum bound both of the labeled terminal fragments of apo-A-I (and $^{125}$I-apo-A-I itself, not shown). As increasing amounts of HDL$_2$ were added, the ability of the antiserum to bind to both of the fragments decreased, but the binding of the COOH-terminal fragment decreased to a proportionally greater extent than did the binding of the NH$_2$-terminal fragment. At maximal absorption with HDL$_2$, only 4% of the original binding capacity for the COOH-terminal fragment remained, whereas 25% of the original amount of the NH$_2$ fragment was still bound.

The anti-NH$_2$-terminal activity of antiserum R 130-3 absorbed with maximal amounts of HDL$_2$ (1000 mg/ml) was also tested as follows (Fig. 3). Constant amounts of $^{125}$I-apo-A-I were added to a series of tubes each of which contained the same limiting amounts of antibody. Increasing amounts of purified NH$_2$-terminal fragment were added to compete with the $^{125}$I-apo-A-I. Similar assays were carried out using unabsorbed antisera R 130-3 at an identical dilution. As increasing amounts of nonisotopic NH$_2$-terminal fragment were added, $^{125}$I-apo-A-I was progressively displaced, but on a molar basis, the NH$_2$-terminal fragment competed -20 times more effectively against $^{125}$I-apo-A-I in the assay containing maximally absorbed antisera than in those containing whole antisera. R 107-3, an anti-HDL$_2$ antiserum was absorbed in identical fashion with HDL$_2$ (not shown). After the addition of as little as 100 mg of HDL$_2$ protein per ml, all capacity to bind HDL$_2$, apo A-I, and its fragments was lost.

**Discussion**

We have previously shown that HDL$_2$-apo-A-I is a less effective inhibitor of the binding of $^{125}$I-apo-A-I to anti-apo-A-I antisera than is isolated apo-A-I (6, 9, 23); also, HDL$_2$-apo-A-I competes more effectively with the $^{125}$I-COOH-terminal CNBr fragment than with the $^{125}$I-NH$_2$-terminal fragment for limited amounts of apo-A-I antisera. These findings suggest that apo-A-I and HDL$_2$-apo-A-I differ in their immunoreactivities and that the COOH-terminal portion of HDL$_2$-apo-A-I is more reactive than the NH$_2$ terminus.

The purpose of one of the sets of experiments reported here (Fig. 1, Table II) was to confirm the relatively greater reactivity of the COOH-terminal portion of HDL$_2$-apo-A-I by studying the specificities of anti-apo-A-I and anti-HDL$_2$ antisera. It was anticipated that if apo-A-I differed from HDL$_2$-apo-A-I, anti-apo-A-I must differ from anti-HDL$_2$-apo-A-I.

The specificities of antisera were characterized in terms of their maximum capacities to bind the $^{125}$I-labeled COOH- or NH$_2$-terminal fragments. The validity of this approach was demonstrated previously when it was shown that anti-apo-A-I antisera were able to bind both the $^{125}$I-labeled terminal fragments of apo-A-I and that antibody populations of corresponding limited specificities (anti-COOH- and anti-NH$_2$-terminal) could be isolated from these antisera by affinity chromatography (9). Thus, the binding of labeled fragments by antisera may be taken as indicating the presence of populations of antibodies of the appropriate specificities. The maximum binding of label should reflect the amount of the given antibody present in the antiserum.

Anti-apo-A-I and anti-HDL$_2$ antisera each precipitated $^{125}$I-apo-A-I, and the $^{125}$I-COOH- and the $^{125}$I-NH$_2$-terminal segments of apo-A-I. However, while anti-apo-A-I antisera bound large amounts of both fragments, anti-HDL$_2$ antisera bound the COOH fragment preferentially. The findings suggest that HDL$_2$-apo-A-I and apo-A-I are dissimilar antigens; furthermore, the COOH-terminal portion of HDL$_2$-apo-A-I is a more potent immunogen than is its NH$_2$-terminal portion, whereas the two terminal portions are nearly equally potent as immunogens during immunization with isolated apo-A-I.

Compatible results were produced by absorption experiments (Fig. 2). The addition of increasing amounts of HDL$_2$ to an anti-apo-A-I antiserum removed antibodies directed against both termini of the apo-A-I molecule, attesting to the fact that both termini of HDL$_2$-apo-A-I are located near or on the surface of HDL$_2$. (Similar conclusions can be reached from the fact that both anti COOH- and anti NH$_2$ terminal antisera could bind intact HDL$_2$ (Table I).) However, during absorption with HDL$_2$, antibodies directed against the COOH-terminal were depleted to a greater extent after addition of absorbant and depleted more completely after exhaustive absorption than were the antibodies directed against the NH$_2$ terminus. This was demonstrated directly in the binding experiment (Fig. 2) and indirectly in the competition experiment (Fig. 3), the results of which interpreted as follows: apo-A-I has several antigenic sites, consequently, anti-apo-A-I antisera contain antibody populations directed against several apo-A-I antigens (9). When $^{125}$I-apo-A-I was added to unabsorbed R 130-3, only a small minority of the binding of $^{125}$I-apo-A-I by antisera R 130-3 took place between antigen-antibody sites which could be inhibited by the NH$_2$-terminal fragment. Therefore, the fragment was a poor competitor. Following absorption with HDL$_2$, antisera R 130-3 had been depleted of many antibody populations, leaving in solution antibody populations of greatly restricted specificities. $^{125}$I-apo-A-I was bound to these remaining antibody populations. The fact that the NH$_2$-terminal peptide was a more effective competitor in this system suggests that the absorbed antiserum was relatively enriched in antibodies directed against the NH$_2$-terminal fragment, i.e., that the antiserum had been depleted of antibodies of other specificities, including the specificity directed against the COOH-terminal fragment. Thus, the COOH-terminal portion of apo-A-I in intact HDL$_2$ is the more potent immunogen and it also removes antibodies from solution more effectively than does the NH$_2$-terminal region. These results strongly support the notion that the COOH-terminal portion of HDL$_2$-apo-A-I is the one more "exposed" on the surface of intact HDL$_2$. 

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