Structure of High Density Lipoprotein

THE IMMUNOLOGIC REACTIVITIES OF THE COOH- AND NH₂-TERMINAL REGIONS OF APOLIPOPROTEIN A-I

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Only 5 to 10% of the apolipoprotein A-I (ApoA-I) of intact high density lipoprotein (HDL) is detectable by radioimmunoassay. In addition, when isolated ApoA-I is recombined with lipids in vitro, its immunologic reactivity is decreased by 30 to 95%. Thus, ApoA-I is less reactive immunologically in the presence of lipids. Our aim was to ascertain whether the COOH- or NH₂-terminal regions of ApoA-I were equally reactive in intact HDL.

CNBr fragments of ApoA-I were produced by the method of Baker et al. (Baker, H. N., Jackson, R. L., and Gotto, A. M. (1973) Biochemistry 12, 3866-3871) and iodinated with lactoperoxidase. Double-antibody radioimmunoassays were set up using anti-ApoA-I antisera and ¹²⁵I-CNBr I (COOH-terminal region) or ¹²⁵I-CNBr II (NH₂-terminal). Both labels were bound by the antisera. Affinity columns were prepared by binding CNBr I or CNBr II to Sepharose 4B. Antibodies specific against CNBr I or CNBr II were isolated by means of these columns, suggesting that ApoA-I had at least two antigenic sites.

In other assays using labeled fragments and anti-ApoA-I antisera, ¹²⁵I-CNBr I was displaced by CNBr I, ApoA-I, and HDL₄ but not CNBr II. Conversely, ¹²⁵I-CNBr II was displaced by CNBr II, ApoA-I, and HDL₄ but not by CNBr I. Thus the assays were region-specific. The reactivities of isolated ApoA-I and the ApoA-I in intact HDL₄ (HDL₄-ApoA-I) were compared in these assays. On a molar basis, HDL₄-ApoA-I was consistently more reactive (2- to 5-fold) in the ¹²⁵I-CNBr I than in the ¹²⁵I-CNBr II assays.

The findings suggest (a) that the two terminal regions of ApoA-I are immunologically distinct, (b) that the two regions can be assayed independently of each other in intact HDL₄, and (c) that the COOH-terminal region is more reactive immunologically than is the NH₂-terminal. The results are compatible with a more "exposed" position for the COOH-terminal region on the surface of HDL₄.

In the last few years, several models of high density lipoprotein structure have been proposed (1-3). All of these postulate that the apoproteins, ApoA-I and ApoA-II, are found on or near the surface of the HDL molecule. However, recently published data show that only about 10% of the mass of ApoA-I, the major protein of HDL, can be detected in intact HDL by radioimmunoassay (4, 5). In addition, when delipidated ApoA-I or HDL protein are recombined with egg lecithin vesicles or HDL lipid, and the recombined particles are assayed for their ApoA-I contents, far less ApoA-I is found than is known to be there (6). These findings suggest that not all of the ApoA-I molecules or all regions of the molecules may be immunologically reactive on the surface of intact HDL. We wished to ascertain whether certain regions of ApoA-I were more reactive than others. Specifically, we wished to explore the immunoreactivities of the COOH- and NH₂-terminal regions of ApoA-I in intact HDL. To do this, it was necessary to ascertain whether the COOH- and NH₂-terminal regions of the ApoA-I molecule could be distinguished immunologically and assayed independently of each other.

Baker et al. (7) have shown that four peptides can be isolated from ApoA-I by cyanogen bromide (CNBr) cleavage. The CNBr I and CNBr II fragments correspond to the COOH- and NH₂-terminal regions, respectively (8). Thus, the aims of this work were (a) to demonstrate that the CNBr I and CNBr II fragments were immunologically distinguishable, and (b) to produce region-specific radioimmunoassays for CNBr I and CNBr II which could be used to "probe" the reactivity of ApoA-I on the surface of intact HDL.

METHODS

Isolation of ApoA-I and ApoA-I Fragments—HDL was isolated from the plasmas of normal donors by ultracentrifugation between the densities 1.090 and 1.21 (HDL₄ was isolated at d 1.070 to 1.12); ApoA-I...
was isolated and purified from delipidated HDL, by column chromatography as described previously (4). These ApoA-I preparations yielded single bands on disc gel electrophoresis in urea (9) and sodium dodecyl sulfate (10); the total amino acid composition, molecular weights (7, 8) were used to calculate the mole amino acid content of Apo-I, CNBr I, and CNBr II solutions. Protein concentrations of HDL solutions were determined by the Lowry procedure (7), using the bovine serum albumin standard. Reaction tubes were extracted with diethyl ether before being analyzed in the spectrophotometer. (The Lowry amino acid mass ratios for Apo-A-I, Apo-II, and ApoC, the proteins which comprised >95% of HDL proteins, were each >0.9 (18); therefore the Lowry procedure probably gives results for HDL protein mass which are accurate to within <10%.) The Apo-I content of Apo-HDL was taken as 65% of Apo-HDL mass. This was based on published data for HDL (4, 11, 19) and our own column chromatographic results with HDL.

RESULTS

We have previously shown that 125I-Apo-I prepared by the chloramine-T method is a satisfactory label for radioimmunoassay purposes (4). 125I-Apo-I prepared by the lactoperoxidase method seems to be equally satisfactory in that, following reprecipitation on Sephadex G-75, the label eluted as a single peak 2 to 3 ml earlier than chymotrypsinogen (molecular weight 25,000, Fig. 2A). This suggests that under assay conditions this label is in its monomeric form. Furthermore, >90% of 125I-Apo-I was precipitable by 10% trichloroacetic acid. A similar precipitability was by antiserum directed against Apo-A-I (Table II).

The 125I-CNBr I purified on Sephadex G-50 and albumin-barbital eluted near the void volume of the column (not shown), suggesting that the label was self-aggregated. To minimize aggregation, the Sephadex G-25 column (used for separation of labeled CNBr I from free 125I) and the Sephadex G-50 column (used for purification of the 125I-CNBr I) were both equilibrated with 0.05 M barbital, pH 8.0. 12SI-ApoA-I prepared by the lactoperoxidase method seems to be equally satisfactory in that, following reprecipitation on Sephadex G-75, the label eluted as a single peak 2 to 3 ml earlier than chymotrypsinogen (molecular weight 25,000, Fig. 2A). This suggests that under assay conditions this label is in its monomeric form. Furthermore, >90% of 125I-Apo-I was precipitable by 10% trichloroacetic acid. A similar precipitability was by antiserum directed against Apo-A-I (Table II).

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The 125I-CNBr II purified by column chromatography on Sephadex G-50 in albumin-barbital or barbital-Triton yielded single peaks which had elution volumes within 2 to 3 ml of that of cytochrome c (molecular weight 12,000, Fig. 2B), suggesting that it was monomeric. The monomeric material reaggregated upon the addition of albumin to the barbital-Triton system. Thus, assays run in barbital-Triton in the absence of albumin probably contained the label in its monomeric form, whereas assays performed in albumin-barbital probably contained aggregated 125I-CNBr I. From 80 to 85% of 125I-CNBr I was precipitated by 10% trichloroacetic acid and 72 to 77% was precipitated by antiserum directed against Apo-A-I (Table II). Similar precipitabilities were obtained by both aggregated and monomeric labels.

The 125I-CNBr II purified by column chromatography on Sephadex G-50 in albumin-barbital or barbital-Triton yielded single peaks which had elution volumes within 2 to 3 ml of that of cytochrome c (Fig. 2), suggesting that the label was present as a monomer in both albumin-barbital and barbital-Triton assays. From 80 to 85% of this label was precipitated by 10% trichloroacetic acid and 72 to 76% by antiserum directed against Apo-A-I. The specific radioactivities of 125I-CNBr II ranged from 12 to 15 mCi/µg. Iodinations were carried out every 15 to 20 days.

The precipitability of both the labeled CNBr I and CNBr II fragments by anti-Apo-I antiserum suggested that the antiserum contained antibody populations directed against both the COOH- and the NH2-terminal regions of the ApoA-I molecule. Indeed two region-specific antibody populations were isolated from these antisera by affinity chromatography (Table II). Antibodies isolated by the CNBr II affinity column precipitated 80 to 85% of 125I-Apo-I and a similar percentage of 125I-CNBr II, but less than 10% of 125I-CNBr I. Conversely, antibodies isolated on the CNBr I affinity column precipitated 90 to 95% of 125I-Apo-I and 65 to 85% of 125I-CNBr I.
Structure of High Density Lipoprotein

Table 1

| Amino acid compositions of apolipoprotein A-I and of CNBr fragments I to IV |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Amino acid                  | ApoA-I | CNBr I | CNBr II | CNBr III | CNBr IV |
|-----------------------------|---------|--------|---------|---------|--------|
| Lysine                      | 19.5 ± 1.9 (19) | 6.4 ± 0.8 (6) | 6.7 ± 1.2 (6) | 2.9 ± 0.1 (3) | 4.4 ± 0.5 (4) |
| Histidine                   | 5.2 ± 0.4 (5)    | 3.9 ± 0.6 (4)    | 4.2 ± 0.5 (4)    | 2.9 ± 0.05 (3) | 3.1 ± 0.2 (3) |
| Arginine                    | 14.9 ± 1.3 (15)  | 9.0 ± 1.0 (8)    | 11.9 ± 0.6 (11) | 4.7 ± 0.6 (5)  | 2.9 ± 0.1 (3) |
| Aspartate                   | 19.9 ± 1.7 (20)  | 5.8 ± 0.6 (6)    | 4.7 ± 0.6 (5)    | 2.9 ± 0.05 (3) | 3.1 ± 0.2 (3) |
| Threonine                   | 10.1 ± 0.7 (10)  | 4.3 ± 0.4 (5)    | 7.5 ± 0.7 (7)    | 11.2 ± 1.0 (12)| 7.2 ± 0.3 (7) |
| Serine                      | 16.0 ± 1.4 (15)  | 5.7 ± 0.8 (6)    | 7.5 ± 0.7 (7)    | 11.2 ± 1.0 (12)| 7.2 ± 0.3 (7) |
| Glutamate                   | 48.9 ± 4.3 (49)  | 13.8 ± 1.6 (15)| 17.8 ± 1.2 (17)| 24.1 ± 1.0 (12)| 9.0 ± 0.1 (1) |
| Proline                     | 9.0 ± 0.6 (10)   | 3.0 ± 0.3 (3)    | 4.6 ± 0.3 (4)    | 2.2 ± 0.1 (2)  | 0.9 ± 0.1 (1) |
| Glycine                     | 11.4 ± 0.8 (10)  | 3.3 ± 0.3 (3)    | 5.2 ± 0.7 (5)    | 2.4 ± 0.1 (2)  | 1.0 ± 0.1 (1) |
| Alanine                     | 19.5 ± 1.8 (11)  | 15.1 ± 1.1 (12)| 3.2 ± 0.4 (3)    | 2.2 ± 0.1 (2)  | 1.0 ± 0.1 (1) |
| Valine                      | 12.3 ± 0.3 (13)  | 3.1 ± 0.4 (3)    | 7.0 ± 1.2 (6)    | 1.1 ± 0.2 (1)  | 1.6 ± 0.3 (2) |
| Methionine                  | 3.0 ± 0.6 (3)    | 1.6 ± 0.1 (3)    | 3.0 ± 0.4 (3)    | 1.0 ± 0.1 (1)  | 0.9 ± 0.2 (1) |
| Leucine                     | 37.6 ± 2.2 (38)  | 16.2 ± 1.4 (16)| 12.7 ± 0.6 (12)| 7.0 ± 0.6 (8)  | 2.9 ± 0.2 (9) |
| Tyrosine                    | 6.5 ± 0.7 (7)    | 2.7 ± 0.2 (3)    | 2.0 ± 0.1 (2)    | 1.0 ± 0.1 (1)  | 0.8 ± 0.2 (1) |
| Phenylalanine               | 5.7 ± 0.8 (6)    | 1.7 ± 0.3 (2)    | 3.0 ± 0.4 (3)    | 0.9 ± 0.2 (1)  | 0.9 ± 0.2 (1) |

* Results are compared to those of Baker et al. (7, 8) which are given in parentheses.
* Methionine is present as homoserine and homoserine lactone that was not quantitated.

Fig. 1. Isolation of CNBr fragments of ApoA-I by the method of Baker et al. (7). Following a 24-hour incubation of ApoA-I (at 23°C) with CNBr (100 mg of protein and 640 mg of CNBr in 10 ml of 70% formic acid), the resulting solutions were diluted with H2O and lyophilized and the product was solubilized (10 ml 0.1 M Tris, pH 8.0/6 M urea/5 ml 25% formic acid) and filtered on Bio-Gel P-30 (A, P30) (2.5 x 90 cm, 25% formic acid, 22 ml/hour, 3.7 ml/tube). Pools I (tubes 31 to 48) and II (tubes 50 to 57) were diluted with H2O and lyophilized. Pool I was dissolved in H2O acidified with formic acid, brought to appropriate pH and conductivity with 0.001 M Tris, pH 8.0/6 M urea, applied to a DEAE-cellulose column (B, DEAE) (0.9 x 30 cm), and eluted with a 5-3 ml gradient (initial buffer, 0.01 M Tris/0.9 M urea, pH 8; final buffer, same buffer plus 0.3 M NaCl, 3.5 ml/tube). Tubes 6 to 14 contained CNBr II and tubes 38 to 43 contained CNBr III. Pool II was dissolved in 3 ml 0.1 M NH4HCO3, pH 8.0, and filtered in the same buffer on a column (1.5 x 30 cm) of Sephadex G-50 (C, G50) (3.5 ml/tube).

Fig. 2. Purification of 125I-ApoA-I, 125I-CNBr II, and 125I-CNBr I by gel filtration using the indicated gels (columns, 0.9 x 30 cm). For the first two labels, columns were equilibrated with 0.06 M barbitol, pH 8.0/0.5% albumin; for 125I-CNBr I, barbitol-0.01% Triton X-100 was used. Elution volumes were compared with those of proteins of known molecular weight and indicated that the labels were in monomeric form.

Further evidence of the immunologic distinctiveness of the two ends of the ApoA-I molecule was provided by using the labeled CNBr fragments in radioimmunoassays. Fig. 3 shows the displacement of 125I-CNBr I by unlabeled CNBr I and Apo-A-I. Over 98% of the added label was displaced by both unlabeled CNBr I and by Apo-A-I. However, the unlabeled CNBr II fragment produced no displacement of counts (Apo-A-II and Apo-C, too, were nonreactive). The converse situation is depicted in Fig. 3B, i.e. the displacement of 125I-CNBr II by unlabeled CNBr II. More than 90% of the added label was displaced in this assay. The curve produced by Apo-A-I closely approximated that of the CNBr II curve, while CNBr I (and Apo-A-II and Apo-C) produced no displacement of counts. These CNBr I and CNBr II assays were run with antiserum R130-3. Similar results were obtained with antiserum R131-2. Furthermore, the assays exhibited the appropriate specificities whether run in albumin-barbitol (as shown) or in barbitol-Triton (not shown).
The immunologic activity of HDL was tested in these assays (Figs. 4 and 5). On a molar basis, the ApoA-I in intact HDL (HDL, ApoA-I) had about 10% of the activity of isolated ApoA-I in competing with 125I-ApoA-I for reactive sites in anti-ApoA-I antisera (4) (Fig. 4A). When the assay was repeated in barbital-Triton (Fig. 4B) instead of albumin-barbital, the reactivity of HDL-ApoA-I was doubled (to ~20% of the activity of ApoA-I).

Where 125I-CNBr I was used as the labeled moiety (Fig. 4C), displacement curves were produced by CNBr I (not shown). ApoA-I, and HDL, HDL-ApoA-I had 37% of the effectiveness of isolated ApoA-I in displacing 125I-CNBr.

With 125I-CNBr II as the label, displacement curves were obtained by CNBr II, ApoA-I, and HDL, but HDL-ApoA-I was only 16% as effective as isolated ApoA-I in displacing the label (Fig. 4D).

The CNBr I and CNBr II assays were repeated with antisera R130-3 (Fig. 5). The displacement curves produced by CNBr I, HDL, and ApoA-I versus 125I-CNBr I were nearly superimposable (Fig. 5A). With 125I-CNBr II as the labeled moiety (Fig. 5B), the curves were farther apart; in fact, HDL-ApoA-I appeared to be only 20% as effective as isolated ApoA-I in displacing 125I-CNBr II. The experiments with R130-3 were repeated three times with two different CNBr fragment preparations with comparable results.

To assess the effect of the state of aggregation of the CNBr I label, assays were performed in barbital-Triton (Fig. 4, E and F). Here HDL-ApoA-I had 63% of the reactivity of isolated ApoA-I in the 125I-CNBr I assay and 38% in the 125I-CNBr II assay. Thus, compared with isolated ApoA-I, HDL-ApoA-I was more reactive in CNBr I than in CNBr II assays, under the several conditions tested. It is worth noting that HDL, displaced all three of the labels more effectively when assays were run in the presence of Triton X-100.

**DISCUSSION**

Given the fact that only a small minority of the potential immunologic reactivity of ApoA-I in intact human and rat HDL is manifest in radioimmunoassays (4-6, 20), it was logical to ask whether the COOH- and NH2-terminal regions of ApoA-I are equally accountable for the poor reactivity. However, it was necessary first to demonstrate (a) that the two terminal regions were immunologically distinct, and (b) that they could be assayed independently of each other. The immunologic heterogeneity of ApoA-I (Point a) was demonstrated by showing that CNBr fragments representing the COOH- and NH2-terminal regions of ApoA-I were both precipitable by antisera directed against ApoA-I (Table II, line 1), and second, by isolating two distinct populations of antibodies from anti-ApoA-I antisera (Table II, lines 3 and 4), one directed specifically against the COOH terminus (CNBr I) and the other against the NH2 terminus (CNBr II). The ability of isolated ApoA-I to stimulate the production of at least two antibody populations implies that ApoA-I contains a minimum of two immunogenic sites corresponding to the two terminal regions (albeit not necessarily identical with them).

To quantify the immunologic reactivity of the two regions (Point b), it was necessary to devise region-specific assays which yielded reproducible results. The specificity of any radioimmunoassay depends on the purity of the labeled moiety (21). Both CNBr I fragments yielded single bands on sodium dodecyl sulfate gel electrophoresis and both had amino acid compositions nearly identical with those reported by Baker et al. (7, 8) (Table I). Most important, there was virtually no cross-reactivity between the two fragments in radioimmunoassays (Fig. 3). Other apoproteins also did not react. Thus, the assays were specific. Reproducibility was adequate within each assay system (Figs. 3 and 5).

The immunologic activities of HDL-ApoA-I relative to isolated ApoA-I were compared in these assays. HDL-ApoA-I was consistently more reactive relative to isolated ApoA-I in the 125I-CNBr I assay than in the 125I-CNBr II assay. Thus, compared with isolated ApoA-I, HDL-ApoA-I was more reactive in CNBr I than in CNBr II assays, under the several conditions tested. It is worth noting that HDL, displaced all three of the labels more effectively when assays were run in the presence of Triton X-100.

**Table II**

| Antibody       | Label          | 125I-ApoA-I | 125I-CNBr I | 125I-CNBr II |
|----------------|----------------|-------------|-------------|--------------|
| Whole antiserum| 81-92          | 72-77       | 70-76       |
| (1:800 to 1:1800) |               |             |             |
| Anti-CNBr I    | 86-87          | 23-43       | <5          |
| (1:50 to 1:100) |               |             |             |

**FIG. 3.** Specificity of the CNBr assays. Displacement curves produced by ApoA-I, CNBr I, and CNBr II in assays using 125I-CNBr I (A) and 125I-CNBr II (B). Both assays contained 3% albumin/0.05 M barbital buffer, and anti-ApoA-I antisera R130-3 (diluted 1:500). The lack of cross-reactivity between CNBr I and CNBr II is evident. Each point was run in triplicate. Coefficient of variation was 4 ± 2% (mean ± 1 S.D.).
FIG. 4. Immunologic activities of isolated ApoA-I and HDL,
ApoA-I. Assays run with antiserum R131-2 (diluted 1:1000 in A and B, and 1:3000 in C to F). Assays A and B contained *51-ApoA-I, C and E contained *51-I-CNBr I, and D and F contained *51-CNBr II. Assays A, C, and D were run in 3% albumin/0.05 M barbital, pH 8; B, E, and F were run in barbital/0.01% Triton X-100. The displacement of each of the labels by isolated ApoA-I and by the ApoA-I in HDL,
is shown (results are expressed in terms of picomoles of ApoA-I; the ApoA-I content of HDL, protein was assumed to be 65% for these calculations). It is evident from the distances between the curves that relative to isolated ApoA-I, HDL-ApoA-I is more effective in displacing *51-CNBr I (C and E) than *51-CNBr II (D and F). Note also that the HDL-ApoA-I displaced all labels more effectively in barbital-Triton (B, E, F) than in albumin-barbital (A, C, D).

FIG. 5. Displacement of *51-CNBr I (A) and of *51-CNBr II (B) by the indicated proteins, using anti-ApoAI antiserum R130-3 (diluted 1:500). Results are given in picomoles of isolated ApoAI or HDL,
ApoAI and picomoles of the appropriate fragments. The displacement
the CNBr I than in the CNBr II assays (Figs. 4 and 5). These findings imply that the conformations of *51-CNBr I and of the COOH-terminal of ApoA-I in HDL, are more nearly alike than are the conformations of *51-CNBr II and the NH2-terminal region. The reasons for this are not known, but one explanation
may be that the COOH-terminal region is more reactive because it is more “accessible” to antibody, perhaps because it is less involved in lipid-protein or protein-protein interactions. Perhaps other factors may be responsible but it is clear that the findings are not due to the differing states of aggregation of
3926 Structure of High Density Lipoprotein

125I-CNBr I and 125I-CNBr II because the differences between HDL-ApoA-I and isolated ApoA-I, although diminished in magnitude, persisted even in assays run in barbital-Triton buffer, where both 125I-CNBr I and 125I-CNBr II appeared to be monomeric.

The ability of Triton X-100 to increase the reactivity of HDL-ApoA-I in each of the assays is an interesting finding, which suggests that the detergent, either by binding to ApoA-I (22) or by some other unknown mechanism, perturbs the structure of HDL so as to make the antigenic sites of ApoA-I more "accessible."

It is anticipated that the use of region-specific radioimmunoassays during controlled perturbations of HDL structure may yield still more information on the structure of HDL.

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Structure of high density lipoprotein. The immunologic reactivities of the COOH-and NH2-terminal regions of apolipoprotein A-I.

G Schonfeld, R A Bradshaw and J Chen

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