\section*{$\beta$-Glycoprotein I}

\textbf{MOLECULAR PROPERTIES OF AN UNUSUAL APOLIPROTEIN, APOLIPROTEIN H}

(Received for publication, June 18, 1982)

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$\beta$-Glycoprotein I ($\beta$GI) has recently been identified as a component of circulating plasma lipoproteins. The metabolic role of this apolipoprotein is not known with certainty; it has been reported that $\beta$GI has a high affinity for triglyceride-rich particles, causing their selective precipitation by detergents, and activates lipoprotein lipase in the \textit{in vitro} hydrolysis of artificial lipid emulsions. In the present report, we have evaluated the secondary, tertiary, and quaternary structure of lipid-free $\beta$GI.

The weight average molecular weight of $\beta$GI, as determined by sedimentation equilibrium measurements, was 43,000 in the presence and absence of denaturing agents. Thus, in contrast to other apolipoproteins, apolipoprotein H (apo-H) does not self-associate in aqueous solution. The circular dichroic spectra of apo-H is unusual in that there are no strong negative bands in the far-ultraviolet region of the spectrum; there is a weak positive maximum at 235 nm and a relatively weak negative maximum at 205 nm. Treatment with guanidinium chloride results in a loss of the positive band with only minor changes in the intensity of the band at 205 nm. Apolipoproteins A-I, A-II, C-I, and E, in contrast, have a secondary structure that contains a high percentage of residues in an \textalpha-helical configuration and undergo major changes in structure at low concentrations of guanidinium chloride.

Highly flexible proteins, such as apolipoproteins A-I, A-II, and C-I, absorb rapidly and reversibly to air-water interfaces, whereas more rigid proteins, such as the classical globular proteins, interact with the interface more slowly and irreversibly. This difference is due to the loosely folded tertiary structure of apolipoproteins and the ease with which they can change structure to accommodate a given environment. The surface activity of $\beta$GI at neutral pH resembles that of typical globular proteins. Treatment with acid or base, although causing only minor changes in the circular dichroic spectra, resulted in major increases in the rate of absorption to an air-water interface; under these conditions the rates of absorption were similar to that found for apolipoprotein A-I. These results are consistent with a more flexible structure for $\beta$GI in acid or base that resembles other loosely folded apolipoproteins.

$\beta$GI associates with plasma lipoproteins and satisfies all of the criteria to be classified as an apolipoprotein. The secondary, tertiary, and quaternary structure of $\beta$GI is, however, quite different from that of other well-characterized apolipoproteins. This difference in structure would be expected to affect protein-lipid interactions; the relationship between apo-H and other apolipoproteins may be similar to that proposed for integral versus peripheral membrane proteins.

Chylomicrons and very low density lipoproteins, secreted by the intestine and liver respectively, are large lipid-protein complexes that are involved in the transport and metabolism of triglycerides, cholesterol, and cholesterol esters. The nascent particles, which are believed to be composed primarily of apolipoprotein B and lipids, gain an additional complement of apolipoproteins upon entering the plasma (for recent reviews, see Morrisett et al., 1977, Scanu et al., 1975, and Osborne and Brewer, 1977). Thus, the distribution of apolipoproteins A-I, A-II, C-II, C-I, C-III, and E is dependent, through the laws of mass action, on the concentration of plasma lipoproteins in plasma. The role of these apolipoproteins in metabolism is not known with certainty; apolipoproteins B and E serve as recognition sites for the specific uptake of plasma lipoproteins by cells, apo-C-II \textsuperscript{1} serves as an activator of lipoprotein lipase (Havel et al., 1973; Brown and Baginsky, 1972; LaRosa et al., 1970; Krauss et al., 1973; Havel et al., 1970) and apo-A-I activates lecithin cholesterol acyltransferase (Fielding et al., 1972). It has recently been established that an additional protein, \textbeta\textalpha-glycoprotein I, is isolatable with plasma lipoproteins. $\beta$GI, which is approximately 18\% by weight carbohydrate, was described originally by Schultz et al. in 1961, and preliminary physical properties were reported by Finlayson and Mushinski in 1967. Approximately 16\% by weight of plasma $\beta$GI is found with chylomicrons and VLDL, 2\% with low density lipoproteins, 17\% with high density lipoproteins, and the remainder (65\%) in the L2 density infranatant (Polz and Kostner, 1979a). Burstein and Legmann (1977) have reported that the selective precipitation of triglyceride-rich lipoproteins by sodium laureyl sulfate or sodium dodecyl sulfate required the presence of $\beta$GI. They suggested ultimately that $\beta$GI was involved in triglyceride metabolism. This same conclusion was reached by Polz and Kostner (1979b) based primarily on the interaction between $\beta$GI and intralipid. More recently, Nakaya et al. (1980) reported that $\beta$GI activated lipoprotein lipase in the hydrolysis of triglyceride-phospholipid emulsions. Since $\beta$GI is isolatable on plasma lipoproteins, it has a high affinity for triglyceride-rich lipoprotein particles, and activates lipoprotein lipase \textit{in vitro}, we have designated $\beta$GI as apo-H.

In view of these recent findings, we have begun a systematic investigation of the interaction of $\beta$GI with triglyceride-rich lipoprotein particles. This work is currently in progress.

\footnote{The abbreviations used are: $\beta$GI, \textbeta\textalpha-glycoprotein I; VLDL, very low density lipoproteins; apo-H, apolipoprotein H; apo-A-I, apolipoprotein A-I; GdmCl, guanidinium chloride.}

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investigation of the interaction(s) between βGI and plasma lipoproteins. A prerequisite to these studies is a more complete understanding of the molecular properties of the isolated apolipoprotein. Previous studies on the molecular properties of apolipoproteins A-I, A-II, C-I, and C-III, have established a framework for characterization of the apolipoprotein components of plasma lipoproteins. Each of these apolipoproteins has a high degree of conformational flexibility and responds dramatically to relatively minor perturbations. Reported molecular interactions that result in changes in secondary structure range from apolipoprotein self-association (Stone and Reynolds, 1975; Vitello and Scamu, 1976; Formisano et al., 1978) and mixed-association (Servillo et al., 1981; Osborne and Brewer, 1980) to the binding of non-polar compounds (Reynolds, 1980). These apolipoproteins also interact rapidly and reversibly with non-polar surfaces, including lipoprotein particles (Pownall et al., 1978; Grow and Fried, 1978; Jonas et al., 1980; Patterson and Jonas, 1980), phospholipid monolayers (Jackson et al., 1980), and air-water interfaces (Shen and Scamu, 1980; Phillips and Sparks, 1980). This ability to adapt easily to a given environment is related presumably to their role in the structure and metabolism of plasma lipoproteins. In the present manuscript, we have evaluated the secondary, tertiary, and quaternary structure of apo-H and compared the solution properties of this unique apolipoprotein with other apolipoproteins.

**Materials and Methods**

**Purification**—Apo-H was isolated from the plasma lipoproteins of a patient with type V hyperlipoproteinemia. Plasma lipoproteins were obtained in ethylamidemaminetetraacetic acid (1 mg/ml), and VLDL (<1,000 g/ml) were separated by ultracentrifugation in a 60 Ti rotor (Beckman Instruments) at 59,000 rpm for 18 h (Havel et al., 1955). VLDL were delipidated with tetramethylurea (Kane et al., 1975), and the soluble apolipoproteins were isolated by heparin Sepharose 4B affinity chromatography by the procedure reported by Sharone and Quarfordt (1977). The fraction containing apo-H was further fractionated by chromatography on Sephacryl S-200. Purity of apo-H was assessed by Ouchterlony immunodiffusion (Ouchterlony, 1967) and by gel electrophoresis in sodium dodecyl sulfate (Weber and Osborn, 1967). Antibodies to apolipoproteins A-I, A-Ⅱ, C-II, E, and H were prepared in rabbits, and the initial protein concentration was determined by absorbance measurements on a Beckman Acta spectrophotometer. Double sector cells with charcoal-fiied Epon blocks were employed throughout; each cell contained 150 ml of sample and 160 ml of appropriate buffer. The surface tension measurements were obtained by initially expelling increasing amounts of solution, allowing the drop to form unaided, and then recording the time for drop formation, as well as weight and volume as given above. The surface tension data presented here were reproducible to with 0,1 dynes/cm.

**RESULTS**

**Purification**—Apo-H, obtained from VLDL, was purified to homogeneity by heparin-Sepharose and Sephacryl S-200 chromatography. The purified apolipoprotein migrated as a single band on sodium dodecyl sulfate gel electrophoresis (Fig. 1a) and formed a single immunoprecipitin line with an antibody prepared against apo-H as well as anti-β-glycoprotein I antibody from Behring Diagnostics (Fig. 1b). The amino acid analysis of purified apo-H was similar to that reported by Heimburger et al., 1964: (moles of amino acid/1000 mol), Asp, 92.2; Thr, 87.6; Ser, 65.0; Gln, 83.9; Pro, 105.6; Gly, 103.8; Ala, 59.5; Val, 52.3; Met, 9.8; Ileu, 36.2; Leu, 61.0; Tyr, 44.6; His, 59.1; Lys, 88.4; and Arg, 33.6.

**Molecular Properties of Apo-H**

The original concentration versus radius profile was analyzed according to the following equation:

\[
\psi = \frac{\phi_{0\omega} \times 119}{10 \times I \times c}
\]

where \(\phi_{0\omega}\) is the observed ellipticity, 119 is the mean residue molecular weight on basis of amino acid composition only, I is the pathlength in centimeters, and c is the concentration of protein in grams/ml. The temperature was maintained at 24°C.

**Surface Tension**—The drop volume method was used for surface tension measurements. The apparatus consisted of a 1-ml Hamilton syringe attached to a metal cylindrical tip of known diameter. The syringe plunger was driven by a micrometer capable of reading to 0.001 ml for accurate volume measurements. In a typical experiment, the metal tip is lowered into the center of a weighing bottle, which is saturated with 1 drop of liquid and preweighed. For surface tension measurements as a function of protein concentration, 4 additional drops of solution are added to the preweighed bottle, and the total weight is then recorded. From the difference between these two weights, the surface tension was calculated according to the following equation:

\[
g \times F \times r
\]

where g is the gravitational force, r is the radius of the metal tip, and F is a function of V/r², where V is the volume of a drop of solution (Harkins and Brown, 1919; Boucher and Evans, 1975). The rate of formation of a drop depends upon the amounts of solution initially expelled from the metal tip (Thornberg, 1978). Time-dependent measurements were obtained by initially expelling increasing amounts of solution, allowing the drop to form unaided, and then recording the time for drop formation, as well as weight and volume as given above. The surface tension data presented here were reproducible to with 0.1 dynes/cm.

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tionapo-Himmunodiffusion of apo-H chloride, concentration values as a function of deviation. The buffers used were: species (see "Materials and Methods".) Values given are ted as the deviation between experimental and theoretical center present case, apo-H is a single homogeneous species of ical data would be a nonrandom function of radius. In the difference between this theoretical profile and the primary ex-perimental data for each cell is illustrated in Fig. 2. If the samples contained detectable species which differed in molec-ular weight, the deviation between experimental and theoret-ical data would be a nonrandom function of radius. In the present case, apo-H is a single homogeneous species of M = 43,000 in the presence and absence of denaturing agents.

Circular Dichroism—The circular dichroic spectrum of apo-H in the far-ultraviolet is illustrated in Fig. 3. The spectrum is unusual for a typical globular protein: there is no strong maximum near 200 nm and no major transitions in the 208–222 nm region. The major features of the spectrum include a positive maximum at 235 nm and a weak negative maximum at 202 nm. The positive maximum at 235 nm is unchanged from pH 7 to 11 and decreases slightly at pH 3 (Fig. 3). The positive maximum is lost with increasing concen-trations of GdmCl (inset, Fig. 3). There is an initial plateau region below 2.0 M GdmCl and the transition is complete by 3 M GdmCl. The low mean residue ellipticity observed at 220 nm would seem to indicate the absence of appreciable residues in a-helical conformation. However, chromophores exhibiting positive ellipticities in the far-ultraviolet could complicate even a qualitative interpretation of secondary structure. Aromatic amino acids, disulfide bonds, and carbohydrate moieties can contribute significant positive ellipticities in the far-ultraviolet region (Woody, 1978; Bewley and Birk, 1978; Coduti et al., 1977; Puett et al., 1977).

Surface Tension Measurements—The profile of surface tension (γ) versus concentration of protein for apo-H, apo-A-I, and chymotrypsinogen is illustrated in Fig. 4. The initial slope of γ versus apo-A-I concentration is much greater than that observed for chymotrypsinogen or apo-H, and the surface pressure (πa−π) at higher concentrations of protein appears to be much higher for apo-A-I. These data represent the surface tension at 1 min, and the differences observed may be due to differences in rate or equilibrium surface pressure.

The time course of absorption for apo-H and apo-A-I is given in Fig. 5. Both the rate of absorption and the equilibrium surface pressure are greater for apo-A-I. Initial protein concentration (from 0.05 to 0.3 mg/ml) had no effect on the equilibrium surface pressure. The initial slopes for both apo-lipoproteins are monoexponential (data not shown) and correspond to rate constants of 2.55 × 10⁻³ s⁻¹ and 9.68 × 10⁻³ s⁻¹, respectively, for apo-H and apo-A-I.

The rate of absorption of apo-H is increased dramatically in acidic and basic solutions (Fig. 5); the rate of absorption of apo-A-I in contrast did not change from pH 3.0 to pH 11.0 (data not shown). The change in rate observed for apo-H does.
not, however, result in a change in the equilibrium surface pressure. Acidification also results in a change in the circular dichroic spectra of apo-H (Fig. 3). The positive maximum at 235 nm decreases slightly in magnitude, and there is a more dramatic increase in negative intensity at 202 nm. The positive maximum at 235 nm is unchanged from pH 7.4 to 11.0; however, there is a decrease in magnitude in the negative maximum and a slight shift to longer wavelengths at pH 11.0.

DISCUSSION

The molecular weight of apo-H in the presence and absence of denaturants, as determined by sedimentation equilibrium, was found to be 43,000 ± 500. Finlayson and Mushinski (1967) reported a $M_w = 48,000$ by sedimentation equilibrium using an assumed partial specific volume of 0.72 ml/g. The partial specific volume of apo-H based on amino acid and carbohydrate composition, as per the Coen and Edsall (1943) procedure, is 0.706 ml/g. With this value, Finlayson and Mushinski's data corresponded to a $M_w = 45,800$. We have measured the partial specific volume of apo-H using the sedimentation equilibrium procedure described by Edelstein and Schachman (1967). Based on the effect of substitution of D$_2$O for H$_2$O on the equilibrium distribution of protein in the analytical ultracentrifuge, this method yields partial specific volumes to within 1% accuracy for homogeneous noninteracting proteins. We obtained a value of 0.706 ± 0.007 for apo-H (0.01 M Tris, 0.1 KCl, 0.001 M azide, pH/pD = 7.4). Thus, the $M_w$ of apo-H is 43,000.

Finlayson and Mushinski, based on experimental sedimentation and diffusion coefficients, computed the molecular weight of apo-H by using the Svedberg equation: $M = RTs/D(1 - v_p)$. The value obtained, 90,000, is appreciably higher than that obtained by sedimentation equilibrium. The reported experimental sedimentation and diffusion coefficients, 2.9 x $10^{-12}$ s and 3.8 x $10^{-7}$ cm$^2$/s, respectively, are both much lower than that predicted using Stokes's law for a sphere of $M_w = 43,000$ and partial specific volume of 0.706 ml/g, $S = 4.75$ x $10^{-13}$ s, and $D_{max} = 9.34$ x $10^{-7}$ cm$^2$/s. These values correspond to fractional ratios ($f/f_0$) from sedimentation and diffusion measurements of 1.63 and 2.46, respectively. Using the treatment of Oncley (1941), where $f/f_0$ is taken to equal the product of two factors, the first depending on hydration and the second on asymmetry, one reaches the conclusion that apo-H must be quite asymmetric. Attributing the observed frictional ratio entirely to hydration requires 16 g of water/g of protein from diffusion data and 2.4 g of water/g of protein from sedimentation data. Both of these values are much higher than that found for most globular proteins (Tanford, 1961). Assuming that hydration amounts to 1 g of water/g of protein, which is an upper limit by most criteria, an axial ratio of 8:1 is needed to account for the frictional ratio obtained from diffusion data.

The high frictional ratios computed for apo-H may also be accounted for by postulating that this molecule is behaving like a random coil, trapping a large amount of solvent within the polypeptide chains. The circular dichroic spectrum of apo-H is complex, however, and cannot be used easily to predict secondary structure. The weak intensity below 210 nm would seem to preclude the presence of appreciable random configurations; however, as indicated above, chromophores or configurations with positive ellipticities in the far-ultraviolet could obscure the large negative values expected for random orientations. Along these lines, we were unable to increase substantially the intensity of the negative maxima with GdmCl or extremes in pH; the weak positive maxima at 235 nm is, however, lost with GdmCl treatment. There is an initial plateau region below 2 M GdmCl and a transition between 2 and 3 M GdmCl resembling the cooperative unfolding of globular proteins.

The above data are thus consistent with at least some ordered structure for apo-H. The effect of proteins on the surface tension of aqueous solutions is also related to conformational flexibility. Proteins that are flexible, such as β-casein, absorb rapidly to air-water interfaces where as more rigid globular proteins, e.g., as lysozyme, absorb slowly. These observed rates of absorption are presumably due to the ease with which these proteins change their conformation and are
unfolded at the air-water interface (Graham and Phillips, 1976). At neutral pH, the rate of absorption of apo-H was comparable to that found for the globular protein chymotrypsinogen; however, the observed rate was 2.6 times slower than that found for apolipoprotein A-I. A rapid interaction between apo-H and an air-water interface is not unexpected. Conformational changes in the presence of lipid have been well documented for apo-A-I over the past decade. The free energy of unfolding apo-A-I (Tall et al., 1976) is also an indication of loosely folded tertiary structure. The secondary structure of apo-A-I also responds to numerous milder perturbations, including protein concentration (Osborne and Brewer, 1980). This apolipoprotein self-associates with concomitant increases in secondary structure with oligomer formation (Stone and Reynolds, 1975; Osborne and Brewer, 1977). Thus, it is not surprising that rapid changes in surface tension are observed in the presence of apo-A-I. Shen and Scaniu (1980) have recently studied the formation of monolayers of apo-A-I at an air-water interface. Their results were consistent with a rapid equilibrium between molecules at the surface and those in bulk solvent. The authors concluded that apo-A-I was unfolded at the surface and attributed the rapid equilibrium to the high degree of flexibility of apo-A-I. Our results are entirely consistent with these postulates. Upon treatment with acid or base, the affect of apo-H on surface tension changes dramatically. At either pH, the rate of change in γ at a given concentration of protein exceeds that found for apo-A-I. This change is accompanied by minor changes in the far-ultraviolet circular dichroic spectra of apo-H. Extremes in pH would be expected to unfold apo-H and generate a more flexible tertiary structure. The absorption of the highly flexible apo-A-I molecule to an air-water interface is independent of pH. These combined data are consistent with acid- and base-induced conformational rearrangements that make apo-H more easily unfolded at an air-water interface, resulting in concomitant increases in the rate of monolayer formation.

The relationships between the affinity of apo-H for an air-water interface and the recently reported affinity for plasma lipoproteins (Burnstein and Legmann, 1977) and intralipid (Polz and Kostner, 1979a) are not clear. At neutral pH, the interaction between apo-H and an air-water interface is comparable to the globular protein chymotrypsinogen. Other apolipoproteins which are known to form integral components of plasma lipoproteins (Shen and Scaniu, 1980) associate much more rapidly with air-water interfaces and result in much higher equilibrium surface pressures. The conformation of these apolipoproteins changes dramatically in the presence of lipid. The secondary and tertiary organization of apo-H, at neutral pH, may be quite similar in the lipidated and lipid-free states, and the relationship between apo-H and other apolipoproteins may be similar to that proposed for integral versus peripheral membrane proteins (Singer and Nicholson, 1972). Along these lines, apo-H has recently been reported to function as an activator for lipoprotein lipase (Nakaya et al., 1980); a more specific secondary and tertiary organization in the presence of lipid may be required for this process. Finally, apo-H may associate with plasma lipoproteins through protein-protein interactions rather than protein-lipid interactions.

In summary, apo-H is a single polypeptide chain of Mr = 43,000 and, in contrast to other apolipoproteins, does not self-associate. The circular dichroic spectra in the far-ultraviolet is unusual with a weak maximum at 235 nm and a relatively weak minimum at 206 nm, and thus the secondary structure of apo-H is quite different from other apolipoproteins. At neutral pH, the affinity of apo-H for an air-water interface is comparable to globular proteins. Treatment with acid or base, although causing only minor changes in secondary structure, results in major increases in affinity for air-water interfaces such that the tertiary structure of apo-H resembles that of the more flexible apolipoproteins (e.g. apo-A-I, apo-A-II, and apo-C-I) under these conditions. Present studies are directed toward the affects of lipid on the secondary and tertiary folding of this unique apolipoprotein.

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