Solubility of Membrane Proteins in Aqueous Media*

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SUMMARY

Human red blood cell ghosts are severely disrupted by the removal of inorganic cations, and in the presence of $5 \times 10^{-3}$ M EDTA or 0.1 M (CH$_3$)$_2$NBr the membrane proteins are almost totally soluble in aqueous media without the use of detergents or organic solvents. These soluble proteins have been partially fractionated by column chromatography as a preliminary step to studying their physical and functional properties. Optical rotatory dispersion spectra indicate no major conformational change upon removal of the proteins from the insoluble lipid in the solvent systems studied. Preliminary investigation of porcine cerebral myelin and bovine heart inner mitochondria suggest that the interaction between lipid and protein differs in these two systems from that in the human erythrocyte membrane.

While the lipids in biological membranes are readily soluble in various organic solvents, attempts to solubilize proteins have, in large part, resulted in “denatured” material. A few exceptions to this include for example the work of Racker (9) who removed active enzymes from inner mitochondrial membrane, Abrams and Baron (10) who isolated soluble ATPase from Streptococcus faecalis by removing Mg$^{2+}$, and Marchesi et al. (11) who solubilized some protein from human erythrocyte ghosts with chelating agents in aqueous media. In all these cases the soluble protein is a small percentage of the total protein and appears to be external to the organized lipid molecules in the original membrane since the extraction procedures leave the lipid bilayer observed in electron microscopy intact. Additional protein still remained in the nonsoluble membrane fraction in all these experiments.

3. Reassociation of the soluble components to form a functioning system. Thus far, no functioning biological membrane has been reassociated from its separated and soluble components, but this is, of course, the ultimate objective.

We have studied human red blood cell membranes according to Items 1 and 2 above with the primary emphasis on the solubility of their protein, or protein-lipid components in aqueous media, or both. The use of detergents and organic solvents has been avoided for two principal reasons. (a) It is important to obtain the proteins or protein-lipid species without inducing major conformational changes or irreversibly “denaturing” these macromolecular components if we are ultimately to study reassociation. (b) Lipids are soluble in both detergents and organic solvents. Important information on the nature of the interaction between proteins and lipids in membranes may be gained if a solvent system is found in which the lipids are not normally soluble but which disrupts the lipid-protein bond and solubilizes protein selectively.

The conditions required for separation of the protein from the major portion of the lipid in the red blood cell ghost suggest an important role for inorganic cations in the structural integrity of this membrane. Over 90% of the protein is soluble in aqueous media under the conditions described herein and can be partially fractionated by column chromatography. The physical properties of these water-soluble proteins indicate an ordered, although not necessarily compact structure.

Since one would like to find some generality in the organization of and forces in biological membranes, we include some preliminary comparative studies on porcine cerebral myelin and bovine heart inner mitochondrial membrane. These investigations suggest differences in the protein-lipid interaction in the three membrane systems.

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‡ The abbreviation used is: SDS, sodium dodecyl sulfate.
**EXPERIMENTAL PROCEDURE**

**Materials**—Human red blood cell ghosts were prepared by the method of Dodge et al. (12). Cerebral porcine myelin was prepared according to the method of Autilio et al. (13). Electron transport particles of bovine heart inner mitochondrial membrane were a gift from Dr. D. E. Green, Institute for Enzyme Research, University of Wisconsin, Madison, Wisconsin. Reagent grade ethylenediaminetetraacetic acid was obtained from Baker and tetramethylammonium bromide from Eastman.

**Methods**—The solubility of proteins from human red blood cell ghosts was determined in two different ways. The freshly prepared ghosts were resuspended in water containing 5 × 10⁻⁴ M sodium azide, pH 7.5, and centrifuged at 48,000 × g to pellet the membrane. No protein or phospholipid was found in the supernatant over the time period of this washing which was never more than 30 min. These ghosts were then suspended in the appropriate solvent at a concentration of 1 mg of membrane per ml and either stirred gently at room temperature or dialyzed against the solvent being investigated. At specified times the suspension was centrifuged at 48,000 × g for 1 hour and the supernatant and pellet analyzed for protein and phospholipid. In a control experiment, the ghosts were suspended directly in the appropriate solvent at a concentration of 1 mg of membrane per ml and dialyzed against the same solvent in a volume sufficient to reduce the original buffer concentration to less than 0.0001 M.

These two methods of investigating the solubility of membrane proteins in various solvent systems produced identical results. No detectable bacterial contamination or proteolysis occurred during the time course of these experiments. Analyses of protein and phospholipid content before and after exposure to solvent were identical within experimental error of ±2%. Polyelectrolyte gels in SDS of the polypeptide chains showed no detectable alteration of the relative amounts in the various molecular weight classes. A few investigations were conducted with lyophilized ghosts in order to determine the effect of dehydration on the solubility properties of the proteins.

Fresh cerebral myelin was treated as described above except that the concentration of membrane was 18 mg per ml. Electron transport particles (inner mitochondrial membrane) were suspended in the appropriate solvent and dialyzed against a sufficient volume to lower the buffer and sucrose concentration residual from the preparation to 0.00025 M sucrose and 10⁻⁵ M Tris-HCl. Membrane concentration in this latter case was 1 mg per ml.

Protein concentrations were determined with the Lowry procedure (14). Phosphorus was analyzed by the method of Bartlett (15).

Optical rotatory dispersion was measured with a Cary 60 recording polarimeter. Gel filtration was carried out on Sephadex G-200 with 5 × 10⁻³ M EDTA, 5 × 10⁻⁴ M sodium azide, pH 7.5, as the eluting solvent.

Polyelectrolyte gel electrophoresis with 5% acrylamide gels in sodium dodecyl sulfate was performed according to the method of Weber and Osborn (3).

**TABLE I**

| Solvent                  | Percentage of protein soluble | Amount of phospholipid per mg protein |
|--------------------------|-------------------------------|--------------------------------------|
|                          | 48 hrs | 72 hrs | 96 hrs | mg               |
| H₂O                      | 35     | 39.9   | 40.0   | 0.09             |
| 5 × 10⁻³ M EDTA          | 48     | 89.0   | 89.0   | 0.18             |
| 10⁻² M EDTA              | 14     | 14.0   | 14.0   | 0.12             |
| 10⁻¹ M EDTA              | 8      | 8.0    | 8.0    | 0.10             |

* Stirred gently. All solutions contained 1 mg of membrane per ml and 5 × 10⁻⁴ M azide.

* Calculated from total phosphorus content assuming phospholipid per phosphorus weight ratio of 25.

**FIG. 1 (left).** SDS-polyacrylamide gel scans of polypeptide chains from human erythrocyte ghosts. Top, superimposed scans from (a) fresh human erythrocyte ghosts and (b) 89% of the erythrocyte protein extracted into 5 × 10⁻³ M EDTA. Middle, erythrocyte protein, 48%, extracted into 5 × 10⁻³ M EDTA. Bottom, erythrocyte protein, 49%, extracted into H₂O (see text for detailed explanation).

**FIG. 2 (right).** Sephadex G-200 gel chromatography in 5 × 10⁻² M EDTA, pH 7.5, human erythrocyte ghost proteins. A 6.5-ml sample containing 1.12 mg of protein per ml, 0.02 mg of phospholipid per ml. Molecular weights of polypeptide chains in pools are marked by arrows (underlined species are major components). With Stokes radii > 35 A: 1, 223,000 and 202,000; 2, 223,000, 202,000, 105,000, 180,000, and 100,000; with Stokes radii of 39 to 33 A: 3, 223,000, 202,000, and 100,000; with Stokes radii of 35.5 to 38.5 A: 4, 128,000, 60,000, and 28,000; with Stokes radii of 30.5 to 33 A: 6, 60,000, 45,000, and 28,000; with Stokes radii of 25 to 30 A: 6, 55,000 and 30,000.
Samples were prepared for electron microscopic examination by suspending the membranes in 6% gluteraldehyde in H2O or in 0.2 mM sodium cacodylate-HCl buffer at pH 7.3. The fixed material was pelleted and postfixed in 4% OsO4 in H2O or in the above buffer. The sample was dehydrated in ethanol and embedded in Epon.

RESULTS AND DISCUSSION

Human Red Blood Cell Ghosts

Solubility of Proteins in Aqueous Media—Fresh human red blood cell ghosts were suspended in varying concentrations of EDTA, 5 × 10^-3 M azide, pH 7.5, as described under "Experimental Procedure." Table I shows the percentage of soluble protein obtained after gentle stirring for 48, 72, and 96 hours at room temperature. It is significant that the maximum amount of protein is solubilized in 5 × 10^-3 M EDTA and that increasing the concentration of this chelating agent reduced the yield of soluble protein. The polypeptide chains found in the supernatant from these experiments were analyzed by SDS-polyacrylamide gel electrophoresis, and some representative results are given in Fig. 1. The water extract contained only the highest molecular weight species with trace contamination by lower molecular weight polypeptides. The 5 × 10^-3 M EDTA extract containing 89% of the membrane protein gave gel patterns identical with that of the intact fresh membrane. (Top one-third of Fig. 1 shows the two superimposed scans obtained by loading identical amounts of protein on gels run simultaneously, and stained and destained under identical conditions.) Furthermore, a comparison of the polypeptides solubilized in 48 hours with those finally soluble in 96 hours suggests that there is not a selective removal of these species under the experimental conditions employed.

Also given in Table I are the phospholipid to protein ratios found in the supernatant. Intact ghosts have a phospholipid to protein weight ratio of approximately 0.7. Note that the soluble species obtained in these experiments have a ratio of approximately 0.1 to 0.2. We do not know at this time if this phospholipid is bound to the protein, but exhaustive dialysis for 10 to 15 days lowers the phospholipid content to less than 0.03 mg per mg of protein.

The effect of the chelating agent, EDTA, on the solubility of proteins from red blood cell ghosts suggests that the interaction of these proteins with the membrane, or membrane lipids, or both, involves inorganic cations. Increasing the EDTA concentration also increases the Na+ concentration, and the reduced solubility in the presence of 0.01 and 0.1 M Na+ EDTA suggests that monovalent as well as divalent inorganic cations may be involved in the overall stability of the structure. If this hypothesis is true, one would expect this interaction to be disrupted by high ionic strength providing the salt does not contain an inorganic cation. We have subjected human red blood cell ghosts to 0.1 M NaCl and 0.1 M tetramethylammonium bromide. When a suspension of ghosts is stirred gently at room temperature for 5 days, in 0.1 M tetramethylammonium bromide, over 90% of the protein is solubilized. SDS polyacrylamide gel electrophoresis of this soluble material gave a pattern identical with that shown in the top of Fig. 1. In contrast, only 10% of the membrane protein is soluble in 0.1 M NaCl under identical experimental conditions.

If lyophilized rather than fresh human red blood cell ghosts are exposed to the solvents discussed above, the rate of solubilization of protein is increased, but the ultimate results are similar. Maximum amounts of protein in soluble form are obtained in 48 hours from lyophilized material as is shown in Table II. Protein, 90%, is soluble in 5 × 10^-3 M EDTA with the percentage decreasing as the Na+ concentration increases. These solutions were subjected to SDS-polyacrylamide gel electrophoresis, and the results were identical with those found with fresh ghost preparations.

Physical Characteristics of Soluble Protein—The proteins extracted into 5 × 10^-3 M EDTA which represent 90% of the total membrane protein were dialyzed for 10 days against the above solvent also containing 5 × 10^-4 M sodium azide. Total protein determined as described under "Experimental Procedure" was identical before and after dialysis and identical polypeptide chain patterns were obtained by SDS-polyacrylamide gel electrophoresis. A 0.5-ml sample of this material containing 1.12 mg of protein per ml and a greatly reduced phospholipid concentration of 0.02 mg of phospholipid per mg of protein was passed down a Sephadex G-200 column with 5 × 10^-3 M EDTA, 5 × 10^-4 M sodium azide, pH 7.5, as the eluting buffer. The eluant diagram is shown in Fig. 2. Pooled fractions were analyzed by SDS-polyacrylamide gel electrophoresis and the results are given in the figure legend. (Some minor components were not detected due to the low concentration present in the eluant, but the total protein eluted from the column was 98% of that applied.) Stokes radii were estimated by calibration of the column with bovine serum albumin, ovalbumin, and a-chymotrypsinogen. Sephadex G-200 is a poor column material for particles with Stokes radii less than

| Solvent | Percentage of protein soluble stirred gently for 48 hrs |
|---------|--------------------------------------------------------|
| H2O     | 48%                                                    |
| 5 × 10^-3 M EDTA | 80%                                                |
| 10^-2 M EDTA  | 41%                                                |
| 10^-1 M EDTA  | 5%                                                  |

Fig. 3. Optical rotatory dispersion of soluble proteins from human erythrocyte ghosts.
have a hydrodynamic shape which is highly asymmetric. This is observed in Fig. 2 where small proteins from the erythrocyte ghost are eluted in overlapping bands between 110 to 145 g of effluent.

The significant information to be obtained from Fig. 2 is the following:

1. The highest molecular weight polypeptide chains, 180,000, 195,000, 202,000, and 223,000 are eluted in the void volume and over a total elution range of 45 to 90 g of eluent. Since the exclusion limit for this gel support is approximately 800,000 for globular proteins, these species are clearly either aggregated or have a hydrodynamic shape which is highly asymmetric.

2. It has been shown (6-8) that over 65% of the membrane protein from human erythrocytes is in two polypeptide chain molecular weight classes, one approximately 100,000 and another approximately 200,000. The 100,000 molecular weight polypeptides are eluted just past the void volume in Fig. 2 and over a range of 80 to 139 g. Thus a partial fractionation of soluble proteins has been obtained. Further work is underway to improve this fractionation by the use of gels with larger pore sizes.

3. The broadness of the elution bands for each molecular weight class of polypeptide chains suggests that some of these chains may be aggregated or may represent different proteins with the same molecular weight but different hydrodynamic shapes.

Optical rotatory dispersion of proteins extracted from human erythrocyte ghosts is shown in Fig. 3. The water extract contains only the four highest molecular weight polypeptide chains. The other two extracts contain all the polypeptides found in the membrane. These curves are very similar to those observed with sonicated suspensions of fresh ghosts (16). There is a minimum in all three curves at 2325 to 2330 A as opposed to 2350 to 2355 A in sonicates. These solutions contained approximately 0.1 mg of phospholipid per mg of protein as opposed to the normal membrane composition of 0.7 mg per mg of protein. It is probable that the small blue shift in the optical rotatory dispersion spectra shown in Fig. 3 as compared to sonicated suspensions is due to a reduction in light scattering as suggested by Urry and Ji (17). The over-all similarity of the spectra of solubilized protein to that of whole ghosts suggests little alteration in the structure on removal of the major lipid portion of the membrane.

An aqueous solution of the four highest molecular weight polypeptide chains from human red blood cell ghosts (0.3 mg of protein per ml of solvent) was titrated between pH 7.5 and 3.0. At pH 5.2 the solution became turbid and at pH 5.0 85% of the protein precipitated. Raising the pH above 6.0 or lowering it below 4.0 resulted in total dissolution of the precipitate.

Electron Microscopic Examination of Insoluble Membrane—Human red blood cell ghosts were suspended in H2O, 5 × 10⁻⁴ M sodium azide, pH 7.5, at a concentration of 1 mg of membrane per ml. The protein, 40%, was solubilized in 48 hours and the phospholipid to protein ratio in the supernatant was less than 0.02 mg per mg. SDS-gel electrophoresis showed that the four highest molecular weight species had been extracted from the membrane. The insoluble pellet from this experiment was examined by electron microscopy following the procedure described under "Experimental Procedure." Half of the pellet was fixed in the absence of buffer and the other half was fixed in the presence of 0.2 M sodium cacodylate. Figs. 4 and 5 show the appearance of the extracted membrane in the absence and presence of 0.2 M Na⁺, respectively. The water-extracted material is badly fragmented and does not form vesicles when fixed in the absence of salt. The addition of buffer on the other hand results in the formation of a large number of vesicles and a total loss of the darkly stained particulate matter seen in Fig. 4. These particles are probably soluble protein and phospholipid contaminants from the supernatant.

A second experiment was performed in which the pellet was fixed in collidine buffer instead of sodium cacodylate. In this case a few vesicles were found, but a large portion of the material was still fragmented or aggregated end to end in a thread-like manner. A control sample of untreated ghosts showed completely intact cells and the routinely observed "railroad track" pattern attributed to lipid bilayers.

### Comparative Solubilities of Proteins from Biological Membranes

Porcine cerebral myelin and bovine heart inner mitochondrial membrane were treated with water, 5 × 10⁻⁴ M EDTA, and 0.1 M tetramethylammonium bromide as described under "Experimental Procedure." The percentage of protein solubilized from these two membrane systems in 48 hours at pH 7.5 and 20° is shown in Table III together with the comparable data from human red blood cell ghosts. It can be seen that the total amount of soluble protein under these experimental conditions is very much less in the cases of myelin and mitochondria than in that of red blood cell ghosts. Other investigators have shown that the basic protein from myelin can be removed in soluble form with aqueous solutions of low pH (18) or 0.4 M ammonium acetate (19). Senior and Brooks (20) solubilized mitochondrial proteins chloroform-methanol extracts by the use of aqueous solutions of low pH (18) or 0.4 M ammonium acetate (19). Senior and Brooks (20) solubilized mitochondrial proteins.

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**Table III**

| Solvent | Human red blood cells ghosts | Myelin | Mitochondria (inner) |
|---------|-----------------------------|--------|----------------------|
|         | Percentage | Amount | Percentage | Amount | Percentage | Amount |
|         | protein    | phosphorus | soluble       | phosphorus | soluble       | phosphorus |
| H2O     | 35         | 0.004  | 3          | N.D.      | 5             | 0.013     |
| 0.006 M | 48         | 0.007  | 8          | N.D.      | 12            | 0.014     |
| 0.1 M (CH₃)₂NBr | 31 | 0.004  | 11         | N.D.      | 14            | 0.004     |

* a Dialyzed 48 hours, 20°, pH 7.5.
* b Not determined.

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**Fig. 4 (top).** Pellet from H₂O-extracted human erythrocyte ghost fixed in absence of salts. Total magnification, × 79,800.

**Fig. 5 (bottom).** Pellet from H₂O-extracted human erythrocyte ghost fixed in 0.2 M sodium cacodylate buffer. Total magnification, × 89,576.
ATPase with high concentrations of EDTA and ATP. However, the important point to be seen in Table III is that under identical conditions the three membranes investigated do not behave in an identical manner. The ratio of phospholipid to protein in the soluble fraction is drastically reduced as compared to the original membrane in the red blood cell ghost extract. However, in the mitochondrial membrane this ratio is nearly the same as that in the intact particle when the extracting solvent is water or $5 \times 10^{-3}$ M EDTA. Only tetramethylammonium bromide solubilizes protein in preference to phospholipid in this system.

Further studies on the solubility of proteins in aqueous media are underway. It is apparent, however, from this preliminary data in Table III that there are significant differences in the interaction forces responsible for the stability of biological membranes.

CONCLUSIONS

The experimental data from a number of previously published investigations has suggested the possibility that inorganic cations play a role in the stability of human red blood cell ghosts.

1. Mazia and Ruby (21) dissolved 90% of the protein from ghosts in aqueous media by lowering the ionic strength of their preparative buffers and including Triton X-100 at one stage in their procedure. (The use of detergent makes it difficult to evaluate the effect of inorganic ions.)

2. Marchesi et al. (11) extracted approximately 30% of the protein from ghosts into aqueous media with a multistep procedure involving chelating agents.

3. A study from Hanahan's laboratory on bovine erythrocytes showed that these membranes are less stable to disruption than the human species due to a lowered concentration of divalent cations in the membrane (22).

4. Rosenberg and Guidotti (23) removed approximately 50% of the membrane protein from human erythrocyte ghosts with sequential extraction with $10^{-3}$ M EDTA followed by 0.8 M NaCl. No polypeptide chain molecular weight analyses were reported for the soluble proteins by these authors. The present investigation shows that 90% of the erythrocyte membrane protein is soluble in $5 \times 10^{-3}$ M EDTA, pH 7.5, with a significant reduction of the phospholipid to protein ratio in the soluble species. The amount of soluble material is reduced by addition of Na$^+$ at concentrations greater than $5 \times 10^{-3}$ M, and more important, 0.1 M tetramethylammonium bromide solubilizes over 90% of the membrane protein while 0.1 M NaCl dissolves only 10%. That inorganic cations play a role in stabilizing the protein-lipid interaction in this system is certainly consistent with all these observations.

Preliminary comparative data on the three membrane systems investigated in this paper do not allow us to make a statement on the effect of inorganic cations on membranes in general. Myelin and inner mitochondrial membrane may also require ionic bridges for stability, but the cations (or anions) involved may be quite different (either in kind or in location) than those in human red blood cell ghosts and thus require different methods of removal. On the other hand, the myelin and mitochondrial systems investigated may be stabilized primarily by hydrophobic bonding or have specific lipid head group-protein interactions which are too strong to be disrupted by 0.1 M tetramethylammonium bromide. These possible alternatives are now being investigated.

The severe fragmentation of human red blood cell ghosts on removal of the four highest molecular weight polypeptide chains and the failure of these fragments to form vesicles such as one would expect if the core of the membrane were a pure lipid bilayer suggest that the protein in this membrane system penetrates the organized lipid structure. Addition of 0.2 M sodium cacodylate resulted in the formation of vesicles with very little remaining fragmented material. Again, this suggests an ionic bridge between protein molecules, lipid molecules, or both in the intact membrane.

Finally, we have described a system in which all of the membrane protein from human erythrocyte ghosts can be solubilized with no major alteration of conformation. These soluble components can be partially fractionated by chromatographic techniques, and this provides us with the first step toward characterization of the role of each protein (structural, enzymatic, etc.) and the eventual reconstitution of the membrane system.

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