WHY HIGH DENSITY LIPOPROTEIN : PHOSPHOLIPID RECOMBINANTS CANNOT BE SPHERICAL MICELLES

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Received 20 August 1979

1. Introduction

The structure of high density lipoprotein (HDL): phospholipid recombinants is of considerable interest, partly because of the possibility that these recombinants might serve as structural and metabolic models for nascent HDL [1]. Based on a number of physical methods of analysis, including gel filtration [2,3] and X-ray scattering [4], the HDL:phospholipid recombinant particle (apolipoprotein A-I:dimyristoyl phosphatidylcholine) has a Stokes radius < 50 Å. In this communication we shall demonstrate by simple geometric arguments that it is impossible for HDL: phospholipid recombinants to be spherical micelles; as a corollary we shall show that these recombinants must be radially asymmetric (e.g., discoidal).

2. Experimental, results and discussion

The maximum diameter of a spherical micelle formed from one molecular species is limited by the length of the amphipathic molecule forming the micelle (fig.1). The DMPC molecule is ~25 Å long when maximally extended. Therefore the maximal diameter of a pure DMPC spherical micelle (an entirely theoretical construct since it would be thermodynamically unstable) is ~50 Å. Studies of the stoichiometry of apo A-I:DMPC recombinant particles suggest that the number of DMPC molecules per particle varies from 80–200 depending upon the protein–lipid ratio [3,5]. The question to consider is whether a spherical DMPC micelle is geometrically capable of containing 80–200 DMPC molecules.

Since the extended length of the fatty acyl chains of DMPC is 18 Å, the nonpolar core of a pure DMPC spherical micelle would be maximally 36 Å in diameter. Given that each pair of fatty acyl chains has a cross-sectional area of 40 Å^2 [6], and omitting any consideration of packing defects, one can calculate that a maximum of 34 DMPC molecules could be packed into a DMPC spherical micelle ($V = 4/3\ \pi r^3$).

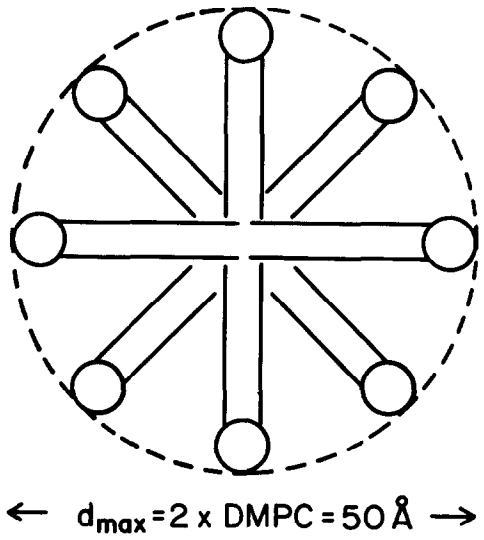

Fig.1. Hypothetical spherical micelle formed from DMPC. The maximum diameter is equal to twice the length of a fully extended DMPC molecule (~50 Å).

Abbreviations: HDL, high density lipoprotein; DMPC, dimyristoyl phosphatidylcholine

Allowing for packing defects [6], the actual number would be less, perhaps 25 DMPC molecules per micelle.

As an even more convincing argument, consider the problem of the packing of the nonpolar faces of the amphipathic helical domains of apo A-I into the nonpolar core of our hypothetical spherical DMPC micelle. Assuming 8 amphipathic helical domains per apo A-I [7–9], an average length of 20 residues per helix [7–9], and 2 apo A-I molecules per recombinant particle [5], the total van der Waals volume of the nonpolar faces would be ~37 000 $Å^3$, which, *reductio ad absurdum*, is greater than the total volume of the nonpolar core of the hypothetical spherical DMPC micelle (25 000 $Å^3$).

Therefore, in order for a spherical DMPC micelle to contain > 25 DMPC molecules and/or 2 apo A-I molecules one of the following must be true: Either the DMPC in the spherical micelle must be compressed beyond its van der Waals limits; or something other than acyl chains (space or protein) must occupy the center of the spherical micelle.

The first possibility can be excluded as physically absurd. Since the possibility of empty space is precluded due to the inexpansible nature of fatty acyl chains in a micellar core and since neutron scattering studies [10,11] as well as the amphipathic helical structure of apo A-I [12] precludes protein in the center of an apo A-I: DMPC micelle, the second possibility is also excluded. (Note that mature HDL, which is spherical, does contain something other than fatty acyl chains at its center, i.e., cholesteryl ester.) Therefore apo A-I:DMPC recombinants with the stoichiometry of 80–200 DMPC molecules and 2 apo A-I molecules per particle cannot exist as spherical micelles.

What then are the possibilities for the structure of apo A-I:DMPC recombinants? A radially asymmetric micelle in the form of an oblate or prolate ellipsoid, in which the minor axis is equivalent to the diameter of the hypothetical spherical DMPC micelle (fig.1) easily allows the packing of > 25 DMPC molecules and/or 2 apo A-I molecules. The final number of molecules is limited only by the length of the major axis. Other more complicated forms, such as star-shaped structures, can be imagined but seem unlikely to be stable. Therefore, on the basis of simple geometric arguments, apo A-I:DMPC recombinant micelles cannot be spherical but must be radially asymmetric in shape. Current experimental evidence favors a discoidal or oblate elliposoidal shape for these recombinants [4,10,11].

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