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Molecular dynamics simulations of a lipovitellin-derived amphiphilic β-sheet homologous to apoB-100 β-sheets at a hydrophobic decane–water interface

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ABSTRACT

Lipovitellin, an egg-yolk lipoprotein, transports lipids in a pocket surrounded by amphiphilic β-sheets. Its X-ray structure provides possibilities to study interactions between lipophilic β-sheets and lipids at the atomic level. Here, we studied a 67-residue-long amphiphilic β-sheet of lipovitellin previously suggested a suitable working model for studies of the lipid-binding behaviour of amphiphilic β-sheet regions in apolipoprotein B-100 (apoB-100). We performed four molecular dynamics simulations with different starting configurations to define characteristics of the amphiphilic β-sheet model at a decane–water interface. In each simulation the model β-sheet bound keenly to the decane layer via its hydrophobic surface. The structural profiles showed unchanged secondary structure of the β-sheet during the attachment. Also, aromatic side chains, especially tryptophans and tyrosines, mediated the attachment to the hydrophobic layer and influenced the orientation of the decane molecules that are in contact with the β-sheet. In conclusion, the present simulations reveal high affinity of a lipovitellin-derived amphiphilic β-sheet to a hydrophobic decane layer. They lay thereby the basis for further studies of the interaction between amphiphilic β-sheets and lipids in complex molecular systems, like LDL particles, in which the large apoB-100 is the main protein component.

1. Introduction

In egg-laying species, lipovitellins are lipid transporters that carry lipids in a specific hydrophobic pocket partly made of amphiphilic β-sheet structures [1,2]. Silver lamprey lipovitellin is a unique X-ray crystallographically defined lipoprotein containing amphiphilic β-sheets. Since lipovitellin is homologous to the N-terminal end of apoB-100, the known X-ray structure of silver lamprey lipovitellin could be utilized in studies of apoB-100–lipid interactions [3,4]. Especially the amphiphilic βD domain, which forms the base of the lipid pocket and closes the lipid cavity in lipovitellin, provides the possibility of studying the interactions between lipophilic β-sheets and lipids at the atomic level.

ApoB-100 is one of the largest single chain proteins known (4536 aa), and it is the main protein component of LDL particles, which are composed of a hydrophobic core consisting of cholesteryl esters and triglycerides, and an amphiphatic surface containing unesterified cholesterol, phospholipids and apoB-100 [5]. Despite major efforts to determine the structure of apoB-100, the atomic details of the structure are still missing [6]. The generally accepted model of the secondary structure of apoB-100 is the so-called pentapartite structure, in which amphiphilic α-helical- and β-sheet-rich regions alternate [3]. This model is in accordance with the recent theoretical model of the tertiary structure of apoB-100 [7]. Previously, it has been proposed that the β-sheet-rich regions of apoB-100 could interact directly with core lipids in LDL particles, and that, contrary to α-helixes, the β-sheets of apoB-100 would have "infinite" lipid affinity [3]. This type of interaction should most likely favor β-sheets over individual strands in LDL particles, resulting in high insolubility of apoB-100 [4]. This proposal agrees with very recent studies indicating that, in general, the hydrophobic faces would be one of the most important factors in the formation of β-sheet folding [8].

In order to shed light on the apoB-100–lipid interactions, experimental studies investigating amphiphilic β-strand binding properties in an oil/water interface [9] and β-sheet formation from β-strands have been conducted [10]. In addition, conformational changes of apoB-100 have been studied at a triolein–water interface, which have implied that apoB-100 is anchored to the lipid moiety of LDL particles through amphiphilic β-sheet-rich regions [11]. However, direct evidence and details of the atomic-level organization of the secondary structures of apoB-100 are still missing.

In this study, we chose a 67-residue-long amphiphilic β-sheet from the βD domain of silver lamprey lipovitellin, originally suggested by Segrest and coworkers as a suitable working model for the

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amphiphilic β-sheets of apoB-100 [3]. We used this β-sheet as a structural model for studying amphiphilic β-sheet interactions at a decane–water interface. First we made comparison between the sequence of the chosen β-sheet model and the entire sequence of apoB-100 using a local sequence homology method. Furthermore, we calculated the electrostatic potential surface of the β-sheet. In order to explore the properties of the chosen model at a hydrophobic decane surface, we performed four lengthy atomic molecular dynamics simulations with different starting conditions. These simulations offer, for the first time, detailed information on and insights into the structure and dynamics of an amphiphilic β-sheet at a hydrophobic layer.

2. Materials and methods

2.1. Amphiphilic β-sheet model

The coordinates of the X-ray structure of lamprey lipovitellin [1,2] were acquired from the Brookhaven protein data bank (PDB entry 1LSH). From the PDB file the residues 1374 to 1440 of lipovitellin were extracted to obtain an amphiphilic β-sheet model of 67 residues (Q_1 G L Q T T L Y Y G L_{11} T S N G L P K A K I_{21} V A V E L S D L S V_{31} W K L C A K F R L S_{41} A H M K A K A A I G_{51} W G K N C Q Q Y R A_{61} M L E A S T), see Fig. 1A. The sequence homology between the model β-sheet and the apoB-100 was determined with ClustalX analysis tools [12], applying standard options (http://bips.u-strasbg.fr/fr/Documentation/ClustalX/).

2.2. Calculation of pK_a values and electrostatic potential surfaces

Sixteen titratable residues are located mainly on the hydrophilic side of the β-sheet, for which the pK_a values in a folded β-sheet environment at the methane lattice were computationally determined by utilizing the MEAD package [13]. A methane lattice of 14×14×2 nm, consisting of 4732 spherical united-atom methane molecules, was constructed and the β-sheet model was sunk halfway into the layer so that mainly the hydrophobic side of the peptide was in contact with the surface. More detailed parameters of the pK_a calculations are given in the supporting information. Methane molecules that were less than 0.29 nm from the β-sheet were removed. The electrostatic potential of the β-sheet model was calculated using the DelPhi program [14,15] provided with the InsightII package (InsightII User Guide, Accelrys Inc., 1995). The

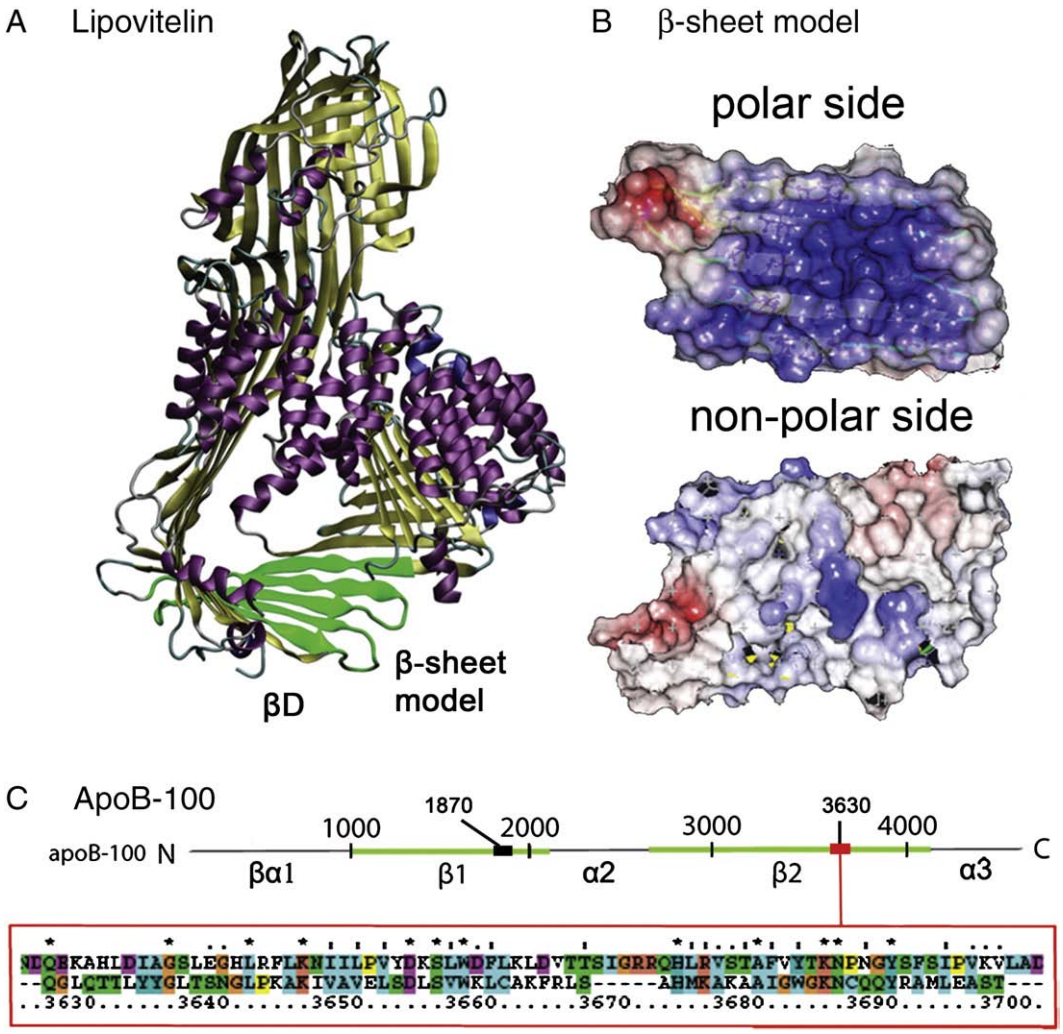

Fig. 1. (A) The X-ray structure of lamprey lipovitellin was acquired from the Brookhaven protein data bank with the accession code 1LSH. The chosen β-sheet model of the βD domain is shown in green. (B) Both sides of the β-sheet model are colored to show electrostatic potential: blue indicates positive and red negative potential. (C) The pentapartite structure of apoB-100 with alternating α-helix-rich and β-sheet-rich regions. The homologous regions between the lipovitellin-derived β-sheet model and the apoB-100 protein are displayed, as determined by sequence analysis tools of ClustalX (red and black box). The pairwise sequence comparison of the red region is also shown.