Molecular Dynamics Study of the N-terminal Domain of Apolipoprotein E on a Mimetic-Lipid Surface

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1 Introduction

Lipid-protein interactions are ubiquitous to living systems. The protein/lipid interface is extremely important but little is known at this time about the specific interactions at these interfaces. In particular the molecular mechanism of apolipoprotein recruitment to lipoprotein surfaces and its subsequent structural alteration is not well understood.

N-terminal domain of human apolipoprotein E (apoE) and apolipophorin-III are exchangeable apolipoproteins that predominantly contain amphipathic α-helical segments. A major conformational change in these proteins is likely to occur upon lipid association, which facilitates interaction with lipid by bringing exposure of the hydrophobic interior of the protein. In apoE the conformational change is supported by surface properties measured at the air-water interface [8] and by more recent fluorescence resonance energy transfer [2]. The opening of the helix bundle in apolipophorin-III upon lipid binding was recently demonstrated by using structure-guided disulfide bond engineering [4].

An understanding of the factors responsible for the protein-lipid association requires their characterization at the molecular level. In this respect computer simulations can help interpreting and rationalizing existing experimental data, which often provide indirect evidence of molecular mechanism, and possibly guiding new experiments.

2 Methods and Results

In this study we examine the impact of a water/organic interface on the structure, dynamics and solvation of apoE by Molecular Dynamics (MD) simulations. Organic phase can be an alternative in computer simulations [3] as well as in experiments [1] to the lipid phase. Of course this representation is crude regarding the headgroup of a phospholipid molecule but it has been demonstrated as a plausible mimetic to correctly orient amphiphilic molecules and to simulate the phase preference of lipophilic molecules. Moreover despite the recent and remarkable successes in MD simulations of pure phospholipid bilayers, it is still very computer-time consuming and a major challenge to simulate a protein interacting with a lipid surface.

An MD simulation of the protein placed in the water phase near a water/organic interface was performed to investigate the structure and dynamics of the system. We compare the dynamical and structural properties of the protein in this simulation to those identified in a trajectory of the lipid-free protein in water. In the latter the protein was shown to behave as a slightly disordered structure [5], a picture that agrees with data of H/D exchange rate [6] and that is analogous to that of the structurally homologous apolipophorin-III, which at physiological conditions adopts a partially folded state with loose tertiary interactions [7].

Though secondary structure dominated by α-helices and helix packing are not significantly affected in the interfacial simulation relative to the aqueous simulation, the protein atoms display higher positional fluctuations in the former. Also the protein backbone gets remarkably more hydrated in the interfacial system than in the aqueous phase. Larger fluctuations and hydration are also more manifest for protein portions close to the interface. This shows a direct correlation between the internal hydration of the apolipoprotein and the presence of a water/organic phase interface, in agreement with experimental data obtained on the structurally similar apolipophorin-III.

The analysis of the water behavior shows that water is more structured in the interfacial region than in the bulk probably to take better advantage of the existing hydrogen-bonding possibilities. In our system one of the hydrogen-bonding potentialities is provided by the protein itself.

These results might be of biological importance for the transition prone to occur in apolipoproteins upon lipid association.

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