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Prediction of the most favorable configuration in the ACBP–membrane interaction based on electrostatic calculations

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ABSTRACT

Acyl-CoA binding proteins (ACBPs) are highly conserved 10 kDa cytosolic proteins that bind medium- and long-chain acyl-CoA esters. They act as intracellular carriers of acyl-CoA and play a role in acyl-CoA metabolism, gene regulation, acyl-CoA-mediated cell signaling, transport-mediated lipid synthesis, membrane trafficking and also, ACBPs were indicated as a possible inhibitor of diazepam binding to the GABA-A receptor. To estimate the importance of the non-specific electrostatic energy in the ACBP–membrane interaction, we computationally modeled the interaction of HgACBP with both anionic and neutral membranes. To compute the Free Electrostatic Energy of Binding (dE), we used the Finite Difference Poisson Boltzmann Equation (FDPB) method as implemented in APBS. In the most energetically favorable orientation, ACBP brings charged residues Lys18 and Lys50 and hydrophobic residues Met46 and Leu47 into membrane surface proximity. This conformation suggests that these four ACBP amino acids are most likely to play a leading role in the ACBP–membrane interaction and ligand intake. Thus, we propose that long range electrostatic forces are the first step in the interaction mechanism between ACBP and membranes.

1. Introduction

The adsorption of macromolecules on different surfaces is an area of experimental and theoretical interest due to the biotechnological and medical applications in which these macromolecules are involved [1]. Despite the wealth of studies in this field, the mechanism of protein–membrane interactions still constitutes an important research area with a myriad of different situations and biological problems still unsolved.

Electrostatic modeling is a computational tool used in biophysical studies given that electrostatics interactions influence or even dominate biochemical reactions. The advances in NMR, X-ray, and cryo-electron microscopy techniques continuously increase the number of biomolecules and multimeric complexes for which atomic coordinates are available. Based on this huge number of data, computational methods have been largely used to extract relevant and meaningful information about the stability, dynamics, and interactions of protein–protein, protein–nucleic acid and protein–ligand systems [2–4].

Among non-specific inter-molecular interactions, protein sequestration at the biomembrane surface is a process that occurs in several cellular pathways. In this respect, the ability of certain proteins to interact with phospholipid interfaces is well known. In several cases, the initial recognition is mainly driven by forces of electrostatic origin and then followed by a variety of events involving protein conformational changes that include the insertion of hydrophobic residues into the membrane.

A novel experimental/computational tool for determination of the configuration of proteins with respect to membranes was recently presented by Tatulian et al [5]. The approach was applied to the human pancreatic phospholipase A2 (PLA2)-membrane complex and involves several experimental techniques like segmental isotope labeling, polarized infrared spectroscopy, protein ligation, among others. In their work the authors coined the concept of "quinary" structure that refers to the rotational and translational positioning of a membrane protein to respect to the membrane.

More recently, an approach based on coarse-grained molecular dynamics simulations was applied to the porcine pancreatic PLA2-lipid bilayer system [6]. Through their perspective these authors show how both electrostatic and hydrophobic interactions determine the location of PLA2 relative to the lipid bilayer, and propose a patch composed of hydrophobic residues surrounded by polar and basic residues as the membrane-binding surface of PLA2.

Aside from the interesting PLA2-membrane system, a number of membrane-associated proteins act in a complex environment formed by the interface between lipid bilayers and bulk water. In this way, antimicrobial peptides bind to anionic membranes [7–9] and also, the

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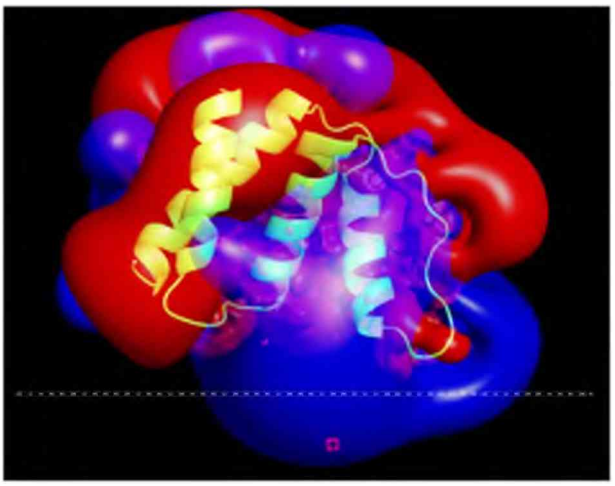

Fig. 1. Electrostatic properties of ACBP from armadillo Harderian gland (HgACBP). The crystal structure shown in ribbons is very similar to other ACBPs and reveals the presence of four -helices. The dashed white line represents the membrane surface. The blue and red surfaces represent, respectively, the +1 kT/e, and −1 kT/e electrostatic equipotential contours calculated by APBS for 100 mM NaCl showing a positive surface surrounding the site proposed as linking to the membrane.

binding of cytochrome *c* to anionic phospholipids is an extensively studied system [1,10,11]. As can be inferred from these examples, due to its physiological importance, protein binding to lipid-water interfaces is an area of increasing research interest, and the knowledge of the initial configuration for the interaction is an important issue in this analysis.

Acyl-CoA binding proteins (ACBPs) are highly conserved 10 kDa cytosolic proteins that bind medium- and long-chain acyl-CoA esters but not fatty acids. They act as intracellular carriers of acyl-CoA and play a role in acyl-CoA metabolism, gene regulation, acyl-CoA-mediated cell signaling, transport-mediated lipid synthesis, and membrane trafficking [12–14]. Also, ACBPs were indicated as a possible inhibitor of diazepam binding to the GABA-A receptor (Diazepam binding inhibitor (DBI)/endozepine (EP)) [15,16], and experimental evidence suggests that ACBPs play a role as regulators of hepatocyte nuclear factor-4α (HNF-4α) [17,18].

The amino acid sequences of over thirty ACBPs, from protozoans, yeasts, plants, insects, reptiles, amphibians, fishes, and mammals, are already known. At this moment, the three-dimensional structure of liver bovine (bovACBP, [19]) (PDBID 2ABD), yeast (yACBP, [20]) (PDBID 1ST7), *Plasmodium falciparum* (PfmACBP, [21]) (PDBID 1HBK), human liver (hLACBP, [22]) (PDBID 2FJ9), and armadillo Harderian gland (HgACBP, [23]) (PDBID 2FDQ) ACBPs are available, and all of them are structurally homologous.

Fig. 1 shows the crystal structure of ACBP from the armadillo Harderian gland (HgACBP) surrounded by surfaces representing the electrostatic properties (see Results and discussion). The crystal structure shown in ribbons is very similar to that of other ACBPs [19–23]. The secondary structure of HgACBP reveals the presence of four -helices, A1 (Glu4-Leu15), A2 (Asp21-Val36), A3 (Gly51-Lys62), and A4 (Ser65-Tyr84) folded into an up-down–down-up helix with a loop between the A2 and A3 -helices. The protein has a shallow bowl-like shape with a hydrophilic region at the rim of the bowl and hydrophobic residues in the loop between A2 and A3 helices. From the three-dimensional structure of holo-bovACBP (palmitoyl-CoA bound), it is known that all four helices are involved in protein–ligand interactions and that the region of binding is the hydrophobic patch at the bottom of the bowl [14]. Although a direct interaction of recombinant mouse ACBP (mrACBP) with membrane has been reported [24], the mechanism of this interaction is still unknown.

The ACBP binding to anionic phospholipid-rich membranes is similar to that of other intracellular LCFA-CoA binding proteins such as sterol carrier protein-2 (SCP-2) and fatty acid binding protein (FABP) [25,26]. Like SCP-2 and FABP, ACBPs have a high affinity for LCFA-CoA, protect LCFA-CoA from microsomal hydrolases, and stimulate microsomal glycerol-3-phosphate acyltransferase. Moreover, it was demonstrated that mrACBP interacts preferentially with anionic phospholipid-rich, highly curved membranes [24].

To assess the importance of the non-specific electrostatic energy in the ACBP-membrane interaction, we computationally model the interaction of HgACBP with both anionic and neutral membranes. To compute the Free Electrostatic Energy of Binding (dE), we use the Finite Difference Poisson Boltzmann Equation (FDPB) method [2]. This study shows that is useful to computationally combine protein and membrane atomic models and an unstructured solvent phase, interacting via electrostatic forces, to get useful hypothesis on the mechanism of protein–membrane interaction. Our results bear relevance for the study of long-chain acylCoA exchange between ACPB and membranes.

2. Materials and methods

2.1. Solvent, membrane, and protein models

Protein and membrane atomic models were considered as rigid bodies, while water and salt ions were modeled together as a continuum structureless medium. Therefore, no internal degrees of freedom (i.e., flexibility of lateral chains, chemical reactions) were taken into account. HgACBP coordinates were obtained from RCSB Protein Data Bank (PDBID 2FDQ, [23]). Membrane coordinates were computationally generated snapshots and equilibrated by molecular dynamics procedures as follow. As a single component of the neutral membrane, we used Dipalmitoylphosphatidylcholine (DPPC), named 0%PS [27], and, for the anionic membrane, we used Dipalmitoylphosphatidylserine (DPPS), named 100%PS [28]. In order to assess the effect of membrane charge, we modeled 1:1 PC/PS bilayers (named 50% PS), 2:1 PC/PS (33% PS), and 3:1 PC/PS (25% PS). To each membrane atom, a radius and a partial charge located at its geometric center were assigned. Parameters were taken from the PDB2PQR server [29], which converts PDB files into PQR files[1], removing steric conflicts and optimizing the hydrogen network. PARSE set of charges were used [30].

The system was mapped onto a three dimensional lattice in which each point represents a small region of the protein, membrane, or solvent. Given that for this system the Debye Length $\lambda_D = 10$ Å, we chose a grid extending 1.3 λ_D from either side of the system, obtaining a grid of 86 Å × 86 Å × 160 Å. The position of the grid during calculations was held constant to allow the self-energy electrostatic terms to cancel.

Single Debye-Huckel boundary conditions were used. This means that the electrostatic potential at the boundary is set to the values prescribed by a Debye-Huckel model for a single sphere with a point charge. The sphere radius was set to the radius of the biomolecule, and the sphere charge was set to the total charge of the protein.

Ion species of opposite equal charges and a radius of 2 Å were modeled as 150 mM NaCl. Atomic partial charges were uniformly distributed.

Molecular surfaces were generated as by Lee and Richards [31] using a 1.4 A probe. A low dielectric constant of 2 is assigned to lattice points that lie within the molecular surfaces of the protein and the membrane, and a high dielectric constant of 78.54 is assigned to lattice points outside the molecular surfaces; the latter region constitutes the solvent (aqueous) phase. We excluded salt ions from a region that

[1] PQR files are PDB files where the occupancy and B-factor columns have been replaced by per-atom charge and radius.

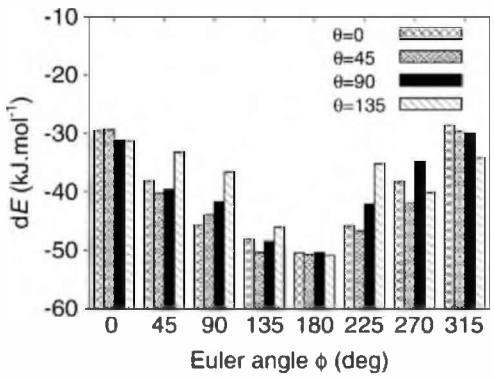

Fig. 2. Electrostatic free energy for the interaction of HgACBP with a 2:1 PC/PS membrane. The figure shows the bar graph of calculated membrane–protein interaction free energy (dE) at a fixed distance r and for different φ (values in abscissa) and θ (values in insert) Euler angles. The plot shows a minimum corresponding to the most favorable configuration.

extends 2 Å (the approximate radius of an ion) beyond the van der Waals surfaces of the protein and membrane.

The kernel of the computational task was carried out by solving the linear Poisson-Boltzmann equation numerically with the aid of APBS code, which is a software package for modeling biomolecular solvation that implements a PMG algorithm [32–34]. To evaluate the Free Electrostatic Energy of Binding (*dE, see below*) for protein–membrane interactions, we also used the Finite Difference Poisson Boltzmann Equation (FDPB) method. This method is one of the most popular continuum models for describing electrostatic interactions in salt solutions [2].

2.2. Electrostatic free energy difference

The solutions of the Poisson-Boltzmann equation were used to calculate the total electrostatic free energy of the system [35]. The electrostatic free energy of the interaction, dE, is the difference between the electrostatic free energy when the protein is close to the membrane and the electrostatic free energy when both protein and membrane are far from each other:

$$dE = \mathrm{E(prot + mem)} - \mathrm{E(prot)} - \mathrm{E(mem)}$$

This energy varies upon changes in the relative positions of the protein and membrane. Eulerian coordinates r, ϕ, θ, and ψ locate the protein with respect to the membrane, with r being the minimum distance between van der Waals surfaces of the protein and membrane atoms. Since the angle describing the protein rotation on a plane parallel to the membrane, is irrelevant in computing the electrostatic free energy of interaction, we only compute dE values with varying ϕ and θ angles. In the same way, since protein translations parallel to the membrane plane do not contribute to energy changes, we ignored the two associated degrees of freedom, thus keeping the molecule right at the middle point in front of the membrane. Therefore, for the electrostatic interaction energy between the protein and membrane, we assume a function $dE = dE(r, \phi, \theta)$, from which we can find the preferred system configuration when the absolute minimum of dE is attained.

2.3. Sampling the electrostatic free energy landscape

To calculate the membrane–protein global energy, we developed a program called ESUP.f in standard ANSI Fortran 77. This program massively generates files in PQR-format (see above) for different positions of the protein–membrane system, and these files serve as input for the APBS program. Automation and processing of data before, between, and after running the programs were carried out with Bash and gnuplot [36] scripting languages. To compute the protein–membrane interaction energy, we sample the configuration space at an interval of $\Delta r = 0.2$ Å for the relative distance, and $\Delta\theta = 45°$ and $\Delta\phi = 1.25°$ for the orientation angle increments.

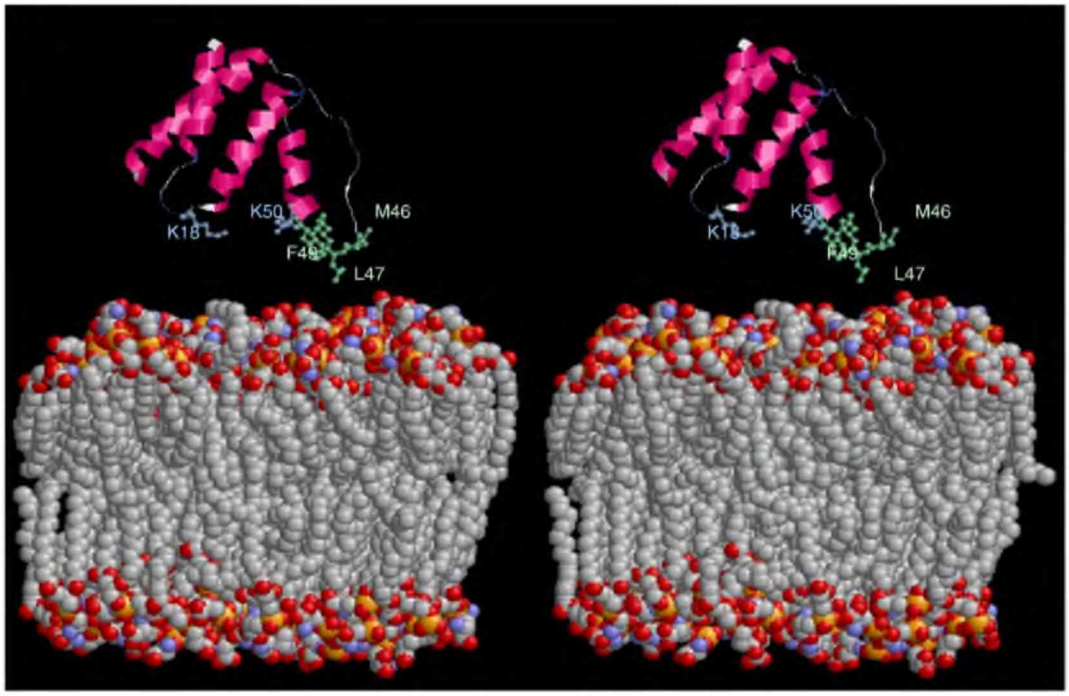

Fig. 3. Stereo view of the membrane-associated orientation for HgACBP, proposed by structural/computational studies. The figure was rendered in Rasmol [42]. The membrane was depicted using red spacefill, Lys18 and Lys50 were represented as cyan sticks and balls, and the conserved hydrophobic residues postulated to penetrate the membrane interface were shown as green sticks and balls.

3. Results and discussion

In this study we computationally modeled the non-specific electrostatic interaction of HgACBP with anionic and neutral membranes made of DPPC and DPPS monomers. This allowed us to determine the most favorable orientation for the ACBP molecule with respect to the membrane, which corresponds to the energy minimum. Fig. 2 shows the calculated membrane–protein electrostatic free energy dE at a protein–membrane distance $r = 3$ Å, and for different φ and θ Euler angles. From these values, we observe that the most favorable orientation corresponds to an angular value $\varphi \approx 180°$. The atomic model corresponding to this configuration is shown in Fig. 3. Fig. 1 shows the electrostatic properties of ACBP in this relative position, with the dashed white line representing the membrane surface. The blue and red surfaces represent, respectively, the +1 kT/e, and −1 kT/e electrostatic equipotential contours calculated by APBS for 100 mM NaCl implemented in VMD [37].

Corresponding to our results, Fig. 3 displays the most favorable orientation between HgACBP and the lipidic membrane. This orientation brings the membrane into close proximity to residues Lys18 and Lys50. Lys18 belongs to the loop, five residues in length, between the α1 and α2 helices. The C-term of the α2 helix contains the hydrophobic residue Leu15, one of the well-conserved amino acids present in all 30 ACBP sequences [14]. It is worth mentioning that, in the majority of these ACBP sequences, and up to three residues apart from Leu15, one to four lysines can be found, thus giving this chain portion a constant positively charged character. On the other hand, Lys50 is located at the N-terminal of the α3 helix, which belongs to triplet-amino acid motif Lys-X-Lys (X = Gly or Ala) conserved in 15 out of 30 ACBP sequences [14]. Therefore, we can conclude that these two positively charged regions highly contribute to the electrostatic interaction energy between the protein and membrane.

Another feature of this membrane–ACBP orientation is that the hydrophobic residues Met46 and Leu47 are in close proximity to the membrane. This orientation will probably favor ligand-binding activity, allowing the fatty acid entry into the ACBP-binding site. This is due to the extension of the hydrophobic groove for binding the acyl moiety from the C-terminus of helix A1 to the N-termini of helices A2 and A3 [22]. This observation is in line with our molecular dynamics results on the interaction between ACBP and the ligand palmitoyl-CoA [38] and in complete agreement with the ACBP-Peripheral-type Benzodiazepine Receptor interaction model previously reported [39].

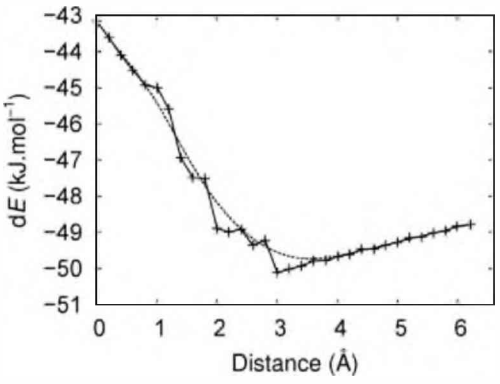

Fig. 4. The electrostatic free energy of interaction is plotted as a function of distance between the van der Waals surfaces of protein and membrane atoms and was determined by solving the Poisson-Boltzmann equation for the HgACBP/membrane system. Zero distance is defined as the configuration in which protein and membrane van der Waal atom surfaces are in contact. In each of the dE calculations, the protein orientation with respect to the membrane remained fixed and only the protein–membrane relative distance (r) was varied. The dashed line shows an approximation with a minimum between 3 and 4 Å.

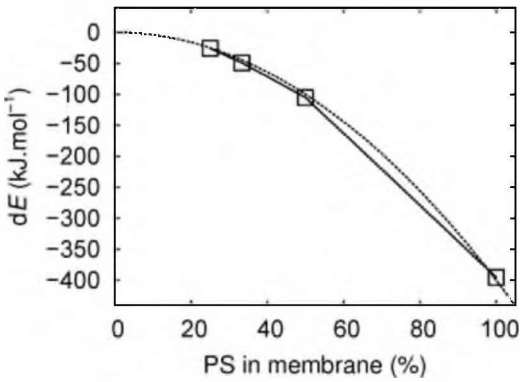

Fig. 5. The HgACBP/membrane electrostatic energy interaction increases sharply as the membrane composition of acidic lipid increases. The squares represent the results obtained with the orientation of the minimum electrostatic free energy, and the dashed line shows the quadratic potential function of approximation. All calculations were done with 100 mM KCl.

In reference to lipid membrane composition, we observe that the interaction is stronger in the case of the anionic DPPS-rich membrane and weaker with the neutral one (100% DPPC). This effect can be seen in Fig. 4, which shows the changes in the minimum electrostatic free energy (dE) as a function of the DPPS/DPPC composition ratio. The electrostatic free energy of interaction dE goes as a simple quadratic potential function

$$dE(x) = -dE_1 x^2, \tag{1}$$

where x is the composition ratio of DPPS/DPPC and dE_1 is the value of the electrostatic free energy of interaction at $x = 1$.

Fig. 5 shows the case for the Hg-ACBP-33% (PS/PC = 1/3) anionic membrane association. The interaction is most favorable at a distance of about 3 Å (the distance between the Leu47 residue and the membrane surface).

From these results, we can deduce that i) the free electrostatic interaction energy selects (like a filter) some preferential ACBP–membrane orientations and ii) the energetically favorable orientations appear to occur in such a way that the hydrophobic residues (in the loop between the α2 and α3 helices) point out to the membrane.

Thus, we postulate that long range electrostatic forces are the first step in the interaction mechanism between ACBP and membrane. Then, upon oriented approximation to the membrane, residues Met46 and Leu47 come in contact with the phospholipid interface. From there on, short range interactions would drive the binding process to completion. In this manner, the affinity of ACBP for biological membranes would be triggered in an electrostatic-dependent manner, then stabilized by a hydrophobic mechanism, and most likely induce protein hydrophobic side chain partitioning into the lipid bilayer. This *electrostatic switch* mechanism has already been proposed in computational modeling studies [40], and it has also been attributed to the membrane protein insertion of the translocation domain of diphtheria toxin [41].

4. Conclusions

Based on our calculations, we deduce that the HgACBP–membrane interaction occurs through a protein–membrane orientation common to neutral and negatively charged membranes. Moreover, our electrostatic model on the HgACBP–membrane system shows that the protein interaction with anionic phospholipid-rich membranes is stronger than with neutral bilayers. This is in complete agreement with the experimental observation of mrACBP previously reported [24], thus allowing us to confirm that continuum electrostatic calculations provide a valuable method to qualitatively describe the interaction between protein and lipid membranes.

In the most energetically favorable orientation (see Fig. 3), HgACBP brings the two charged residues Lys 18 and Lys 50 and hydrophobic residues Met46 and Leu47 into membrane surface proximity. This conformation suggests that these four ACBP amino acids are most likely to play a leading role in the ACBP–membrane interaction and ligand intake.

Acknowledgments

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