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High-Resolution Structural Studies Elucidate Antiatherogenic and Anti-Inflammatory Properties of Peptides Designed to Mimic Amphipathic α-Helical Domains of Apolipoprotein A-I

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Abstract

Peptides designed to mimic the antiatherogenic and anti-inflammatory properties of apolipoprotein A-I show that although lipid association is required, not all lipid-associating peptides exhibit these properties. Our studies of a series of peptides showed that peptides with aromatic residues at the center of the nonpolar face were able to interact with inflammatory lipids and inhibited inflammation, which resulted in the amelioration of several lipid-mediated disorders such as lesion development, tumor formation, and Alzheimer's plaque formation. The pK_a values determined using ^{13}C nuclear magnetic resonance (NMR) spectroscopy of K residues located at the polar-nonpolar interface provided the first clue to the relative orientations of the peptide helices with respect to each other and around the edge of the lipid discoidal complexes. High-resolution ^{1}H-NMR studies of peptide-lipid discoidal complex confirmed the amphipathic α-helical structure of the peptide, location of aromatic residues of the peptide closer to the polar-nonpolar interface, and head-to-tail arrangement of the peptide helices around the edge of the disc. Amphipathic α-helical structure and the location of aromatic residues (F, W, Y) closer to the polar-nonpolar interface in a lipid environment allow the peptide to strongly bind oxidized lipids resulting in its anti-inflammatory properties.

Keywords

amphipathic α-helix; apolipoprotein A-I; HDL; lipid; lipoprotein; NMR; oxidized lipid; peptide

Lipoproteins are macromolecular complexes of proteins (called apolipoproteins) and lipids. Whereas lipids, especially cholesterol, being primarily hydrophobic in nature, are insoluble in water, lipoproteins circulate as water-soluble apolipoprotein-lipid complexes. Among lipoproteins, high levels of low-density lipoprotein (LDL) and very low-density lipoprotein

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are atherogenic, whereas high levels of high-density lipoprotein (HDL) are antiatherogenic. HDLs are apolipoprotein A-I (apoA-I) rich lipoproteins. The mechanism by which apolipoproteins keep lipids water soluble, especially highly hydrophobic triglycerides and cholesterol esters in the apolipoprotein-lipid complexes, was not known till the theory of apolipoprotein-lipid interaction in plasma lipoproteins mediated through amphipathic α-helices in apolipoproteins was proposed.[1]

Most of the antiatherogenic action of HDL appears to be due to its major apolipoprotein component, apoA-I with 243 amino acid residues. The gene structure of this apolipoprotein indicates that it consists of repeating units of 22mer and 11mer domains, most of them punctuated by Pro. Research in our laboratory was initiated to understand the structure of apoA-I and other apolipoproteins that are responsible for keeping the lipoproteins soluble in plasma. Molecular modeling clearly showed that several regions of apolipoproteins, when folded as an α-helix, form a secondary structure with a distinct segregation of polar and nonpolar faces. Such a structure, termed an amphipathic α-helix, is well suited to interact with both polar aqueous environment and nonpolar lipid environment in plasma lipoproteins.[2]

Determination of the Amphipathic α-Helical Structure

We surmised that if the amphipathic α-helical structure is responsible for solubilizing lipids, then even small peptides that can adopt this secondary structure should solubilize lipids in an aqueous environment. Computer analysis revealed that most of the helices in apolipoproteins showed a particular pattern of amino acid distribution, in which basic residues (R and K) are located at the polar-nonpolar interface and negatively charged residues are located at the center of the polar face. Such amphipathic helices were called class A helices.[3]

The first peptide designed to mimic the amphipathic helical domains of apoA-I was 18A with the sequence DWLKAFYDKVAEKLKEAF.[4,5] This peptide has no sequence homology to any of the known amphipathic helical domains of exchangeable apolipoproteins. 18A was able to solubilize 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) to form discoidal peptide-lipid structures that were similar in size and shape to those formed by apoA-I and DMPC. Based on these observations and the ability of these complexes to efflux cholesterol from cells and activation of the enzyme lecithin:cholesterol acyltransferase (LCAT), 18A was termed apoA-I mimetic peptide.[4,5]

The addition of an acetyl group at the N-terminal and an amide group at the C-terminal in 18A produced a peptide that was called Ac-18A-NH_2.[6] The Ac-18A-NH2 showed a much greater potency in raising the bilayer to hexagonal phase transition temperature of dipalmitoleoyl phosphatidy-lethanolamine compared to 18A.[6] In this regard, Ac-18A-NH2 more closely resembles the behavior of the apoA-I, a potent inhibitor of lipid hexagonal phase formation. The activation of the plasma enzyme LCAT by Ac-18A-NH_2 peptide is also greater than 18A and comparable to that observed with apoA-I.[6]

To better understand the role of interfacial basic amino acid residues, the microenvironments and titration characteristics of Lys residues in Ac-18A-NH_2 were examined using ^{13}C

nuclear magnetic resonance (NMR) spectroscopy.[7] Lys-4, −9, −13, and −15 in Ac-18A-NH_2 associated with DMPC had pK_a values of 11.0, 9.4, 9.4, and 10.3, respectively.[7] The measured pK_a values are consistent with Lys residues 4 and 15 being present in a polar microenvironment whereas Lys residues 9 and 13 are present in a less polar microenvironment.[7]

A high-resolution ^{1}H-NMR structure of Ac-18A-NH_2 in a 50% (v/v) trifluoroethanol-d_3/water mixture, a membrane-mimetic environment, indicated that in addition to N-terminal acetyl and C-terminal amide groups, the amphipathic α-helical structure of Ac-18A-NH_2 is further stabilized by interactions between the hydrophobic residues on the nonpolar face of the helix.[8]

To determine the lipid-associated structure of Ac-18A-NH_2, we undertook high-resolution ^{1}H-NMR studies of the peptide-DMPC complex.[9] This study confirmed that the peptide adopts a well-defined amphipathic α-helical structure associated with the lipid in a 1:1 (mass:mass) peptide:lipid ratio. Nuclear Overhauser effect spectroscopy (NOESY) revealed a number of *intermolecular* close contacts between the aromatic residues in the hydrophobic face of the helix and the lipid acyl chain protons. The pattern of observed peptide-lipid nuclear Overhauser effects (NOEs) was consistent with a parallel orientation of the amphipathic helix, with respect to the plane of the lipid bilayer, on the edge of the disc. Based on the results of chemical cross-linking and molecular modeling, we proposed that peptide helices are arranged in a head to tail fashion to cover the edge of the disc. This arrangement of peptides is also consistent with the pK_a values of the Lys residues determined previously.[7] Taken together, these results provide, for the first time, a high-resolution structural view of the peptide-lipid discoidal complexes formed by a class A amphipathic α-helical peptide.[9]

Substitution of 2 Leu residues on the nonpolar face of Ac-18A-NH_2 (renamed as 2F because of the presence of 2 F residues on the nonpolar face of the helix), L-3 and L-14, with F residues produced the peptide 4F (so named because of 4 F residues on the nonpolar face of the helix) (Figure 1).

The 4F peptide has been extensively studied for its superior anti-inflammatory and antiatherogenic properties compared to 2F. Like 2F, 4F also forms discoidal nascent high-density lipoprotein-like particles with DMPC. We undertook high-resolution ^{1}H-NMR studies to deduce the detailed structure of 4F in 4F:DMPC disc. Like 2F, 4F adopts a well-defined amphipathic α-helical structure in association with the lipid at a 1:1 (mass:mass) peptide:lipid ratio. NOESY experiments revealed a number of *intermolecular* close contacts between the aromatic residues in the hydrophobic face of the helix and the lipid acyl chain protons. Similar to 2F, the pattern of observed peptide-lipid NOEs is consistent with a parallel orientation of the amphipathic helix, with respect to the plane of the lipid bilayer, on the edge of the disc. However, in contrast to 2F in 2F:DMPC complex, 4F in the 4F:DMPC complex is located closer to the lipid headgroup as evidenced by a number of NOEs between 4F and DMPC headgroup protons. These NOEs are absent in the 2F:DMPC complex. In addition, the conformation of the DMPC *sn-3* chain in 4F:DMPC complex is different than in the 2F:DMPC complex as evidenced by the NOE between lipid 2.CH and βCH_2 protons

in 4F:DMPC, but not in 2F:DMPC, complex. Based on the results of this study, we inferred that the antiatherogenic properties of 4F may result from the preferential interaction of certain amino acid residues with the lipid headgroup.[10] A molecular model of 4F:DMPC complex is shown in Figure 2.

Peptides with Aromatic Residues Clustered at the Center of the Nonpolar Face Strongly Bind Oxidized Lipids

Whereas 4F administration into dyslipidemic mice inhibited atherosclerosis lesion development, 2F peptide administration did not. 4F peptide was able to interact strongly with oxidized lipids and converted proinflammatory HDL into anti-inflammatory, whereas 2F peptide was not very effective.[11,12] Compared with L, F possesses about 12% larger hydrophobic surface area[13] and shows a preference for the water-lipid interfacial region.[14] It is worthy of note that aromatic rings of F, W, and Y contain π-electrons that can participate in cation-π interactions.[15] Model building supported the idea that whereas Leu residues at the center of the nonpolar face in 2F allow the peptide to insert deeper in the more hydrophobic lipid environment, peptides with aromatic F residues at the center of the nonpolar face, like 4F, are less deeply buried and reside in the less polar hydrophobic environment. Oxidized lipids being more polar than the unoxidized lipids also reside in a less hydrophobic environment thus bringing them closer to the peptides with aromatic residues clustered on the nonpolar face. In support of this, whereas 4F inhibits LDL-induced monocyte chemotaxis, 2F does not.[11] In addition, presence of W at the polar-nonpolar interface also contributes to redox properties of the peptides. It should be noted that W and Y in membrane proteins are localized at the polar-nonpolar interface.[16,17] This arrangement of W and Y amino acids has been implicated in stabilizing the membrane structure from oxidation.[18] In the designed peptides, W is located at the polar-nonpolar interface and Tyr is at the center of the nonpolar face. Indeed, we have shown that although W residue in 4F is modified by oxidizing agent such as hypochlorous acid (HOCl), the peptide retained its lipid association and cholesterol efflux properties.[17] Thus, presence of W at the interface retained the amphipathic nature of the peptide including its biological properties even after oxidative modification of W.[19]

The surprising observation that a 10-residue class G* peptide from apolipoprotein J, (113–122)apoJ, with the sequence Ac-LVGRQLEEFL-NH_2, possesses anti-inflammatory and antiatherogenic properties prompted us to delineate its structural characteristics in the presence of normal and oxidized lipid. Toward this, we determined the high-resolution structure of (113–122)apoJ peptide in solution using high-resolution ^{1}H-NMR spectroscopy and studied its interaction with lipids, including oxidized lipids, using a number of biophysical methods. Circular dichroism and NMR studies established that in the presence of dodecylphosphocholine (DPC) micelle, this peptide adopts amphipathic α-helical structure. The observed NOEs indicated that the amphipathic helical structure of the peptide is stabilized by the N-terminal acetyl and C-terminal amide blocking groups. We used isothermal titration calorimetry to measure the binding enthalpy of the peptide with DPC micelle, an oxidized lipid, 1-(palmitoyl)-2-(5-keto-6-octene-dioyl) phosphatidylcholine (KOdiA-PC), and the mixture of these 2 lipids (5 mol% KOdiA-PC in DPC micelle). We

found that peptide binding with DPC micelle is associated with an enthalpy change (−16.75 ± 0.16 kcal/mol) much larger than that resulting from the binding with KOdiA-PC (−3.67 ± 0.13 kcal/mol). Incorporation of a small amount of KOdiA-PC (5 mol%) in DPC micelle also results in the lowering of peptide binding enthalpy (−13.43 ± 0.18 kcal/mol). These results are consistent with an overall negative charge and altered conformational properties of oxidized *sn*-2 chain of KOdiA-PC. Our results unambiguously established the amphipathic α-helical structure of (113–122)apoJ peptide in the presence of DPC micelle as well as its ability to bind oxidized lipid. These in vitro results help explain the previously observed anti-inflammatory and antiatherosclerotic properties of this peptide.[20]

Sidedness of R Residues in apoA-I Structure and Design of Mimetic Peptides

We performed alignment of apoA-I sequences from 31 animal species.[21] We found that there is a specific conservation of salt bridge-forming residues in the first 30 residues of apoA-I and general conservation of a variety of residue types in the central domain, helix 2/3 to helix 7/8. In the lipid-associating domain, helix 7 and helix 10 are the most and least conserved helices, respectively. Furthermore, 8 residues are completely conserved: P66, R83, P121, E191, and P220, and 3 of 7 Y residues in human apoA-I, Y18, Y115, and Y192, are conserved. Residue Y18 appears to be important for assembly of HDL. E191-Y192 represents the only completely conserved pair of adjacent residues in apoA-I; Y192 is a preferred target for site-specific oxidative modification within atheroma, and molecular dynamic simulations suggest that the conserved pair E191-Y192 is in a solvent-exposed loop-helix-loop. Molecular dynamics testing of human apoA-I showed that M112 and M148 interact with Y115, a microenvironment unique to human apoA-I. Finally, conservation of R residues in the α11/3 helical wheel position 7 supports several possibilities: interactions with adjacent phospholipid molecules and/or oxidized lipids and/or binding of antioxidant enzymes through cation-π orbital (aromatic) interactions. We conclude that sequence alignment of apoA-I provides unique insights into apoA-I structure-function relationship.[22]

To test the hypothesis that sidedness of interfacial R residues in apoA-I mimetic peptides, similar to that observed in apoA-I,[22] may be important for biological activity, we compared the properties of 4F and analogs, [$K^{4,15}$→R]4F and [$K^{9,13}$→R]4F, with K→R substitutions on the right and left sides, respectively, of the 4F amphipathic helix. Intraperitoneal administration of these peptides into female apoE null mice (n = 13 in each group) reduced *en face* lesions significantly compared with controls; 4F and [$K^{4,15}$→R]4F were equally effective whereas [$K^{9,13}$→R]4F was less effective. Turnover experiments indicated that [$K^{4,15}$→R]4F reached the highest, whereas [$K^{9,13}$→R]4F had the lowest plasma peak levels with a similar half-life as the [$K^{4,15}$→R]4F analog. The half-life of 4F was 2 times longer than the other 2 peptides. The order in their abilities to associate with HDL in human plasma, generation of apoA-I particles with pre-β mobility from isolated HDL, lipid associating ability, and sensitivity of lipid complexes to trypsin digestion was: 4F>[$K^{4,15}$→R]4F>[$K^{9,13}$→R]4F. These studies supported our hypothesis that the sidedness of interfacial R residues in the polar face of apoA-I mimetics results in differential biological properties.[21]

HDL-associated paraoxonase-1 (PON1) is crucial for the antioxidant, anti-inflammatory, and antiatherogenic properties of HDL. Discoidal apoA-I:1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) complex has been shown to be the most effective in binding PON1, stabilizing it, and enhancing its lactonase activity as well as its inhibitory activity of LDL oxidation.[23] Based on our earlier study demonstrating that apoA-I mimetic peptide 4F forms discoidal complex with POPC, we hypothesized that lipid complexes of 4F would be able to bind PON1 and enhance its activity and stability. To test our hypothesis, we expressed and purified a recombinant PON1 (rPON1) and studied its interaction with 4F:POPC complex. Our studies showed significant increase, compared to the control, in the paraoxonase activity and stability of rPON1 in the presence of 4F:POPC complex. We proposed that 4F:POPC complex is a novel platform for PON1 binding, increasing its stability, and enhancing its enzyme activity. In addition, we proposed a structural model for the 4F:POPC:PON1 ternary complex that is consistent with our results and other published observations.[24]

Design of Shorter apoA-I Mimetic Peptides and Interaction with Lipid

The lipid interactions of 2 apoA-I-derived class A amphipathic peptides, 14A (Ac-DYLKAFYDKLKEAF-NH_2) and 18A (Ac-DWLKAFYDKVAEKLKEAF-NH_2), including the disc-like supramolecular structures they form with phospholipids, have been reported recently. Thus, the topologies of 14A and 18A in phospholipid bilayers have been determined by oriented solid-state NMR spectroscopy. Whereas at a peptide-to-lipid ratio of 2 mol% the peptides align parallel to the bilayer surface, at 7.5 mol% disc-like structures are formed that spontaneously orient in the magnetic field of the NMR spectrometer. From a comprehensive data set of 4 ^{15}N- or ^{2}H-labeled positions of 14A, a tilt angle, which deviates from perfectly in-planar by 14°, and a model for the peptidic rim structure have been obtained. The tilt and helical pitch angles are well suited to cover the hydrophobic chain region of the bilayer when 2 peptide helices form a head-to-tail dimer. Thus, the detailed topology found in this work agrees with the peptides forming the rim of nanodiscs in a double-belt arrangement.[25] An important observation is that the head-to-tail orientation of these peptides around the edge of discoidal structure strongly support the interaction of π-electron containing aromatic rings for the stabilization of discoidal structures.

Interaction of Amyloid Beta (1–40) Peptide with 4F and 4F-Lipid Nanodiscs Inhibits Its Aggregation

Oral administration of 4F to an Alzheimer's mouse model improves cognitive function and reduces amyloid burden.[26] Whereas one of the mechanisms is decrease of oxidative effects of amyloid deposits in the brain, another function could be direct interaction with amyloid beta-40 or −42 peptides inhibiting amyloid aggregates. Soluble amyloid beta peptide can then be cleared from the brain in the form of soluble 4F-amyloid beta peptide complex. In support of this, 4F both in lipid-bound and lipid-free states has recently been shown to significantly delay amyloid beta (1–40) (Aβ40) peptide aggregation.[27] A substantial change in Aβ40 conformation occurs upon 4F binding through electrostatic and π-π interactions.[27] 4F peptide was found to interfere with the central β-sheet-forming residues of Aβ40 through

substantial hydrogen, π-π, and π-alkyl interactions.[27] Results of these studies suggest development of 4F as a potential amyloid inhibitor.

Conclusion

Among the peptides designed to mimic the properties of apoA-I, the peptides designed to interact with oxidized lipids appear to be most effective in ameliorating various lipid-mediated disorders. In the presence of lipid, these 18 residue anti-inflammatory peptides adopt an amphipathic α-helical structure, reside close to the water-lipid interface, and bind oxidized lipids strongly. Strong interaction of the peptide with oxidized lipids is facilitated by the location of aromatic residues (F, W, Y) of the peptide closer to the polar-nonpolar interface in a lipid environment. This results in the conversion of proinflammatory HDL into anti-inflammatory and inhibition of LDL-induced chemotaxis. Based on the structural characteristics of biologically active peptides that we delineated, it may be possible to design peptides shorter than 18 amino acids with antiatherogenic and anti-inflammatory properties.

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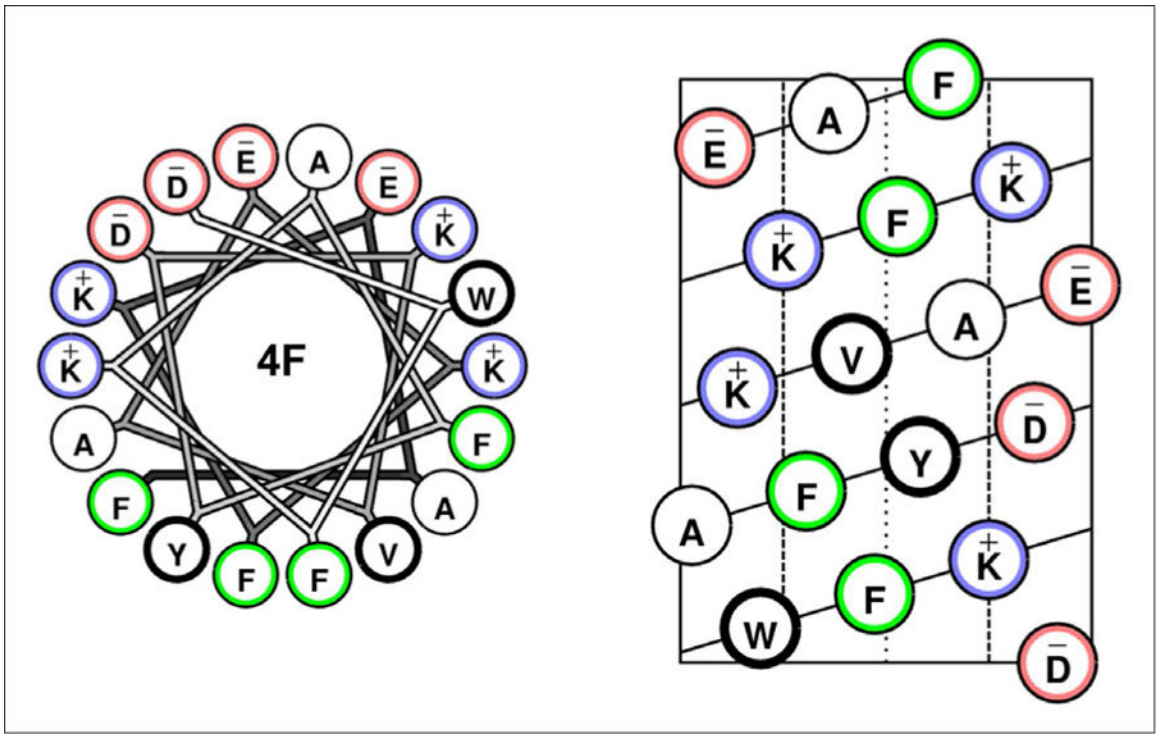

Figure 1.

Helical wheel (**left**) and helical net (**right**) diagrams of 4F. Clustering of 4 F residues (shaded in green) on the nonpolar face of the helix is worthy of note.

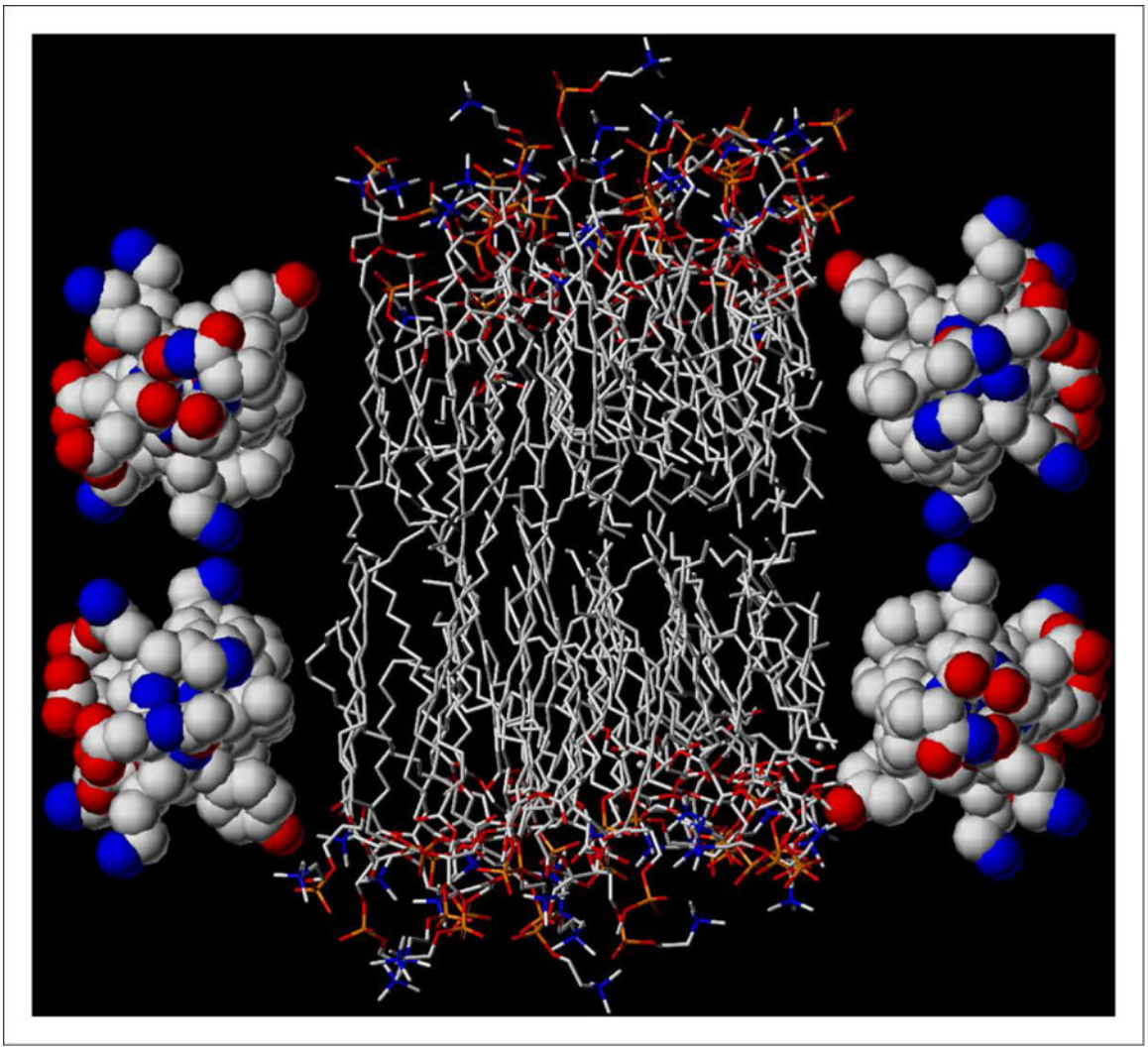

Figure 2.

A molecular model of 4F:1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) complex derived from the high-resolution ^{1}H nuclear magnetic resonance studies of the complex.[10] 4F helices are shown in space filling model and a portion of the DMPC bilayer is shown in the stick model for clarity. 4F helices are arranged in a head-to-tail manner parallel to the plane of the lipid bilayer. This arrangement of 4F helices stabilizes 4F:DMPC nanodiscs in an aqueous environment by shielding the hydrophobic portion of the lipid bilayer through the hydrophobic face of 4F helices.