Lipid-peptide interactions and membrane stability

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A new class of peptides that associate with lipids in membranes, commonly known as "oblique-orientated peptides", has recently been described. Due to an asymmetric distribution of hydrophobic residues along the axis of the α-helix, such peptides adopt an oblique orientation which can destabilize membranes or lipid cores, thereby facilitating cellular processes such as vesicular fusion or protein transport across subcellular compartments, as well as remodelling of lipid cores. Fusogenic peptides were not only found in viral proteins, but were also identified in other membrane-destabilizing proteins such as the β-amyloid peptide involved in Alzheimer's disease, the sperm-egg fusion protein, and in the signal sequence of secretory proteins. Fusogenic peptides were also found in the plasma cholesteryl ester transfer protein CETP, in the microsomal transfer protein MTP, in lecithin cholesterol acyltransferase, and in apolipoprotein A-II. Although active fusogenic peptides were described as α-helices, conformational studies reported a β-sheet structure for lipid-associated fusogenic peptides. We synthesized a series of fusogenic peptides with varying sequences and monitored vesicle fusion by following lipid mixing using fluorescent probes. The conformation of the lipid-associated peptides was studied by Fourier-transform infrared spectroscopy, while that of lipid-free peptides was measured in aqueous buffer/ trifluoroethanol mixtures by circular dichroism. These data show that lipid binding and fusogenic activity are higher for the peptides with a strong tendency to form aggregated β-sheets in lipids, and that the most active fusogenic peptides insert into lipids as α-helices and subsequently convert into more stable β-sheets in membranes.

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