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Peptide-Membrane Interactions. Electrostatics and Cooperativity.

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High-sensitivity isothermal titration calorimetry (ITC) has opened a new avenue to efficiently study the mechanisms of peptide-membrane interaction. A wide variety of interactions has been found which range from hydrophobic insertion *(cyclosporin A,* an immuno-suppressant) over electrostatic adsorption *(somatostatin,* a peptide hormone; *nisin, a* bacterial antibiotic; *substance P,* a pain transmitter) to cooperative P-structured aggregation at the membrane surface *(*β *APP(1-40),* a peptide of Alzheimer plaques) and membrane induced random coil -> a-helix transitions *(magainin,* an antibiotic; *ApoAI, a* lipoprotein involved in lipid transport). A comparison of the thermodynamic data reveals a graded transition from entropy-driven to enthalpy-driven reactions.

The thermodynamics of the helix-coil transition at the membrane surface was investigated with the antibiotic *magainin 2 amide (M2a).* The helix content of *M2a* was systematically varied by substituting two adjacent amino acids by their D-enantiomers. The thermodynamic parameters of *M2a* binding to the membrane are linearly related to the helicity. Helix formation can be described with the Zimm-Bragg theory, is a strong driving force of peptide insertion into the membrane, and accounts for about 50% of the free energy of binding.

A cooperative process is also found for βAP(1-40), a major component of Alzheimer plaques. ITC and circular dichroism detect a random coil ↔ b-sheet aggregation at the surface of negatively charged membranes. The cationic peptide is attracted to the membrane surface. The increase in peptide concentration together with the membrane surface acting as a template then leads to the formation of large β-structured aggregates.