Peptide-induced permeation of model membranes by antimicrobial peptidomimetics

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Antimicrobial peptides (AMPs) usually interact with cellular membranes, disrupting their integrity, and so, as a consequence of their target, the development of resistance to AMPs is much less likely to occur. Thus, the search for new membrane-active peptides is a current thrust in research and AMPs can be considered lead compounds for the development of a new class of antibiotic pharmaceuticals. Peptaibols are a family of naturally occurring AMPs that bear α,α-dialkylglycines such as Aib, Iva and Deg in their sequence [1-5]. These tetrasubstituted amino acids give peptides more defined conformations and more resistant to biodegradation as they are not recognized by hydrolytic enzymes [6].

The shortest member of the peptaibol family, Peptaibolin (Ac-Leu-Aib-Leu-Aib-Phol), has been the subject of recent *in silico* studies that suggest that its membrane affinity might be increased by replacement of Aib by other α,α-dialkylglycines, more structurally constrained and hydrophobic [7].

In the present communication, a set of Peptaibolin and several peptidomimetics incorporating unnatural α,α-dialkylglycines (Deg, Dpg, Ac_6c) were studied for their ability to interact and permeate model membranes from phosphatidylcholine/cholesterol, in different ratios. The permeation activity was monitored by fluorescence spectroscopy, following the release of encapsulated 6-carboxyfluorescein. The collected data suggested a relationship between the structure of the unnatural α,α-dialkylglycines (bearing longer and bulkier side chains) and the capacity of the corresponding peptidomimetic to permeate the model membranes.

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