Membrane active peptides with unnatural amino acids: permeation studies in model membranes

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The 20th century was marked by scientific developments that changed our society. In medicine, the major developments were vaccines and antibiotics, which lead to proper treatment and, in some cases, eradication of several diseases. However, antibiotic availability and their indiscriminate use prompted bacteria to the development of resistance. To address this issue the scientific community turned their interest into natural antimicrobial peptides (AMPs) which are ubiquitous components of the innate defence mechanisms, known to be active against bacteria, fungi and protozoans usually by interacting with microbial membranes and leading to the disruption membrane integrity [1]. Among AMPs, peptaibols are a family of natural peptides bearing α,α-dialkylglycines such as Aib, Iva and Deg in their composition. These tetrasubstituted amino acids give peptides more defined conformations and more resistant to biodegradation as they are not recognized by hydrolytic enzymes [2,3].

Peptaibolin (Ac-Leu-Aib-Leu-Aib-Phol) is the smallest member of the peptaibol family. Recent *in silico* studies suggest that membrane affinity might be increased by the substitution of the Aib residues by more structurally constrained and more hydrophobic α,α-dialkylglycines [4].

Herein we report the membrane permeation studies of Peptaibolin and several mimetics incorporating unnatural α,α-dialkylglycines (Deg, Dpg, Ac_6c) with model membranes (egg phosphatidylcholine/cholesterol, in different ratios). The permeation activity was monitored by fluorescence spectroscopy, following release of an encapsulated fluorescent probe (6-carboxyfluorescein). The obtained results revealed a correlation between the length and bulk of the side chain of the unnatural α,α-dialkylglycines and the ability of the corresponding peptide to permeate the model membranes.

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