NMR-DERIVED RESTRAINED MOLECULAR DYNAMICS USED TO STUDY BINDING OF PEPTIDES TO BILAYER MEMBRANE MODELS.

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The structure of membrane acting peptides is relatively easy to solve but frequently not able to fully explain its biological function. The reason is that they display plastic and dynamic structures and accommodate differently in diverse membrane mimetic systems.

PW2 is a cationic peptide selected from phage display libraries showing anticoccidial activity. It acts disrupting the coccide membrane. It is flexible when free in solution, and gains structure upon interface binding.

We determined by NMR the structure of PW2 in SDS and DPC micelles, and also studied features of PW2 free in water, showing that it is ordered in the aromatic region, which contains the anchoring-motif WWR, a common feature in these three different systems.

However the equilibrium dynamics between the free and bound form of micelles (ms) and bilayers (hours to days) is quite different and the behavior of peptide in this way has different features.

With that in mind we decided to study PW2 structure in phosphatidylcholine (PC) containing phosphatidylethanolamine (PE) - PC:PE (1:1) vesicles. The interaction occurs reaching a fast exchange regime, becoming possible perform transfer NOESY spectrum. The NOESY was fully assigned and a structural tendency of peptide in this environment was calculated.

The membrane interaction was studied using chemical shifts, paramagnetic relaxation enhancement and restrained MD. The structure showed the motif WWR playing an important role in the interaction with PCPE interface. Different from the interaction with the micelles, Ile12 is interacting with the vesicle interface. We concluded that Ile12 could be a key residue for specificity and WWR the anchoring motif.

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