04.01 – Molecular Structure and Biological Activity


Ion transport across biological cell membranes is an area in which structural studies can play an important role. To this end, the availability of a molecule for which high resolution crystallographic studies can be correlated with functional properties is needed. Gramicidin, a 16 residue hydrophobic polypeptide synthesized by B. brevis, is an ideal model system. Crystallographic studies of its complexes with ions have given us insight into the nature of the interactions between the polypeptide backbone and the transported ligand. Studies of its complexes with lipids give us insight into the nature of its interactions within the membrane. A high resolution structure of the complex of gramicidin with calcium chloride has been determined. A number of other calcium complexes have now been found to produce other crystal forms which have cavities at different sites along the length of the pore. These structures give rise to a series of "snapshots" pictures of the ion being transported, which are forming the basis of our molecular simulation studies. Recent studies have examined complexes between gramicidin and other monovalent cations of different sizes, and of different valencies. All of these crystallographic studies are complemented by our spectroscopic studies which have examined the dynamics of the interaction of gramicidin with ions of different sizes. Thus, this relatively small molecule which acts as an ion channel provides the most complete data to date on structure/function relations for ion transport in membranes. (This work has been supported by grants from the U.S. National Science Foundation and the S.E.R.C. of the U.K.)

MS-04.01.02 STRUCTURAL STUDIES ON BIOACTIVE PEPTIDES. By G. Prégent, F. Lido, S. Géofre and P. Picard, Laboratoire de Cristallographie, Université de Bordeaux I, 33405 Talence, France.

Among the bioactive peptides, one of the widely studied families is constituted of the asparagine pro tease inhibitors.

There are two strategies for the design of such inhibitors: the replacement of the asparagine peptide bond of a substrate with other nonhydrolysable moieties, or the substitution of a usual endocyclic amide bond by an unusual one.

All the aspartic proteases are known to be inhibited by pepstatin A (isovaleryl-Val-Val-Ala-Ala-NH₂), where (Ala) is (Lys)-3,4-amino-3-hydroxy-6-methylheptanoic acid. Statine has been found to be essential for inhibitory potency of pepstatin and is widely used in the design of inhibitors.

In spite of the great interest of statine, only a limited number of X-ray diffraction studies has been carried out on statine alone and on statine containing peptides. However, the number of conformations observed in the crystal state is large enough to allow a study aimed at determining the main conformational preferences of statine and the conformational role of its two additional main chain carbon atoms.

MS-04.01.03 DESIGN, STRUCTURE AND ACTIVITY OF CONFORMATIONALLY SPECIFIC PEPTIDES. By T.P. Singh, Department of Biophysics, All India Institute of Medical Sciences, New Delhi 110029, India.

α,β-dehydro-amino acids have emerged as a very effective tool in the design of specific peptide structures. These residues occur naturally in a variety of peptide antibiotics and in some proteins. The peptides can be prepared in the laboratory with substitutions of α, β-dehydro-residues at desired sites. Our investigations suggest that a dehydro-residue adopts three sets of site specific φ, ψ values: φ,ψ if dehydro-residue is at (i-2) position, -60, 140° while at (i-1) and

and φ,ψ in a sequence of dehydro-residues separated by one or two saturated residues. Therefore, a β-turn II, β-turn III and a 3₁₀ helical conformations can be produced very specifically. The dehydro-Ala with only methylene group at the Cα position adopts an extended chain conformation and in a peptide sequence gives rise to a mixed β-strand structure similar to those observed in many proteins. These studies thus, offer a highly promising and effective principle of peptide design.

MS-04.01.04 MOLECULAR STRUCTURE AND BIOLOGICAL ACTIVITY: TRANSMEMBRANE-INHIBITOR BINDING INTERACTIONS AS A TARGET SITE MODEL. Vivian Cody. Medical Foundation of Buffalo, 73 High St., Buffalo, NY 14223 USA.

Recent structure-activity data show that many pharmacological agents are strong competitors for thyroxin (T₄) binding to transthyretin (TTR), a serum thyroxin hormone transport protein. Furthermore, the marked similarity in the structural features required for relative binding affinity to TTR and activity of thyroid-responsive enzymes such as inducible dihydro-orotate (TPO), Ca²⁺-ATPase of membrane T₄ transporters suggests homology between the TTR hormone binding site and these enzyme active sites. To understand how diverse classes of molecules such as indolylacetic analogues, plant flavonoids, insecticidal diterpenes and benzodiazepines can act as inhibitors of TTR binding, computer graphic modeling studies of inhibitor structures were carried out. Crystallographic analysis of thyroxin hormones reveals that the tyrosyl 3,5-diones cause the diphenyl ether to adopt a skewed conformation, whereas removal of this bulk releases this constraint. Flavonoids, a broadly distributed class of hydroxy substituted phenyl benzopyrones or benzofuranes plant pigments, are also potent inhibitors of TTR hormone binding and TTD activity. Although these structures have less conformational flexibility and even in general planar, computer graphic modeling data suggest homology between the hormone phenolic ring and that of the flavones and reveal that the flavones can bind in the TTR hormone site. From these studies the benzoflavone, EME 21,988, was designed as a potent TTR and TTD inhibitor. To test this model, the structure of TTR-flavone complexes were undertaken and reveal a complex binding pattern which indicates the flavones have multiple binding modes to TTR. Mitronone (2-methyl-5-cyano), 4-biphenyl (6)-5-flavone and aminin...