04–Crystallography of Biological Small Molecules

04.01 – Molecular Structure and Biological Activity

MS–04.01.01 THE STRUCTURES OF TRANSMEMBRANE CHANNELS. B.A. Wallace*, D. Doyle, B. Hussain-Bates, and R.W. Janes. Department of Crystallography, Birkbeck College, University of London, London WC1E 7HX, U.K.

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 functioal 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 caesium chloride has been determined. A number of other caesium complexes have now been found to produce other crystals forms which have caesiums at different sites along the length of the pore; these structures give rise to a series of "snapshot" 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 divalent cations. All of these crystallographic analyses are complemented by our spectroscopic studies which have examined the dynamics of the interactions 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. Précigoux*, S. Llido, S. Geoffre 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 aspartyl protease inhibitors.

There are two strategies for the design of such inhibitors: the replacement of the scissile peptide bond of a substrate with other nonhydrolysable moities, or the substitution of a usual endogenic aminoacid by an unusual one.

All the aspartic proteases are known to be inhibited by pepstatin A (isovaleryl - Val - Val - Sta - Ala - Sta), where (Sta) is [(4S,3S)-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 -10029, 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: $80,0^{o}$ if dehydro-residue is at (i+2) position, $-60, 140^{o}$ while at (i+1) and $\pm 60 \pm 30^{o}$ in a sequence of dehydro-residues separated by one or two saturated residues. Therefore, a β-turn II, β-turn III and a 3_{10} -helical conformations can be produced very specifically. The dehydro-Ala with only methylene group at the C^{β}-position adopts an extended chain conformation and in a peptide sequence gives rise to a mixed β-strand structure similar to those observed in large loops of proteins. These studies, thus, offer a highly promising and effective principle of peptide design.

MS–04.01.04 MOLECULAR STRUCTURE AND BIOLOGICAL ACTIVITY: TRANSTHYRETIN-INHIBITOR BINDING INTERACTIONS AS A TARGET SITE MODEL. Vivian Cody, Medical Foundation of Buffalo, 73 High St., Buffalo, NY 14203 USA.

Recent structure activity data show that many pharmacological agents are strong competitors for thyroxine (T_4) binding to transthyretin (TTR), a serum thyroid 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 iodothyronine deiodinase (ITD), Ca^{2+}-ATPase or membrane T_3 transporter suggests homology between the TTR hormone binding site and these enzyme active sites. To understand how diverse classes of molecules such as iodothyronine analogues, plant flavones, inotropic bipyridines and benzodiazepines can act as inhibitors of TTR binding, computer graphic modeling studies of inhibitor structures were carried out. Crystallographic analysis of thyroid hormones reveals that the tyrosyl 3,5-iodines 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 benzofurones plant pigments, are also potent inhibitors of TTR hormone binding and ITD activity. Although these structures have less conformational flexibility and are in general planar, computer graphics 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 bromoflavone, EMD 21388, was designed as a potent ITD and TTR inhibitor. To test this model, the structures of TTR-flavone complexes were undertaken and reveal a complex binding pattern which indicates the flavones have multiple binding modes to TTR. Milrinone (2-methyl-5-cyano(3,4'-bipyridin)-6-(1H)-one) and amrin-

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