Protein conelations between its structural features and binding and activity by a grant from the antagonists show data for a larse number of naturally occurring and synthetic mutants. Janes, Dept. of Crystallography, Birkbeck College, the C-terminal helix. Comparisons of the crystal stucture with the STRUCTURE OF HUMAN found using current drophobic binding pockets. Information about the growing family of proteins related to theStructure of human endothelin-1 the most potent naturally-occuning and synthetic mutants. The most significant differences are in those regions with 1639 protein atoms, 65 rapamycin atoms, and pock­ket between a large amphipathic a-helix. The struc­ture shows extensive interactions between rapamycin and both proteins but only modest protein-protein interactions. The structure also provides, among other things, an understanding of the critical nature of the serine 2,053 residue, and the first structural information about the growing family of proteins related to the ataxia telangectasia mutant (ATM) gene product. Crystals of the triple complex form in space group P212121 with a = 44.63, b = 52.14, and c = 102.53 Å and one FKBP12-rapamycin-FRB complex in the asymmetric unit. Data were collected to 2.7 Å with a rotating anode source. A phasing model was found using MR (FKBP12) and SIRAS (HgCl2 derivative). The current model has R = 19.3% (Rfree = 29.9%) for the 6206 reflex­tions between 8 and 2.7 Å and good geometry (r.m.s. deviations of 0.008 Å for bond lengths and 1.48° for bond angles) for a model with 1639 protein atoms, 65 rapamycin atoms, and 23 solvent at­oms—not counting hydrogens.

MS05.01.02 THE RELEVANCE OF THE CRYSTAL STRUCTURE OF HUMAN ENDOThELIN TO G-PROTEIN COUPLED RECEPTOR BINDING. B.A. Wallace and R.W. Janes, Dept. of Crystallography, Birkbeck College, University of London, London, England

The recently solved (Nature Struct. Biol. 1:311-319) crystal structure of human endothelin-1 the most potent naturally-occurring vasoconstrictor, has revealed structural features of the polypeptide that differ considerably from those found in the reported structures of endothelin as determined by NMR spectroscopy (Prot. Sci. 4:75-82). The most significant differences are in those regions important for receptor binding and specificity, namely the central loop and the C-terminal helix. Comparisons of the crystal structure with the structures of chemically-unrelated but very potent small molecule antagonists show (FEBS Lett 374:379-383) a strong correspondence in their 3-dimensional structures. These, and correlations between its structural features and binding and activity data for a large number of naturally-occurring and synthetic mut­ants strongly support the crystal structure as being biologically relevant with respect to binding to G-Protein coupled receptors. (Supported by a grant from the British Heart Foundation).

MS05.01.03 CONSTRAINED LINEAR OPIOID PEPTIDES. Jeffrey R. Deschamps, Clifford George, Christi Moore, Robert Cutney*, and Judith L. Flippen-Anderson, Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC, 20375 and *Hampton Research, Laguna Hills, CA.

A new class of potent site selective opioid peptides has been developed which consist entirely of aromatic amino acids and contain a conformationally restricted phenylalanine residue (i.e. tetrahydroisoquinoline-5-carboxylic acid, Tic) in position 21. More recent work on these short linear peptides has shown that aromaticity of residues 3 and 4 is not required for high binding affinity. Members of this family that contain a L-Tic residue in position 2 are δ selective antagonists and those that contain a D-Tic at position 2 are agonists with some preference for μ receptors. Even the dipeptide (Tyr-Tic-NH2) has been shown to possess substantial opioid activity. We have determined the structures of several members of this new class of opioid peptides. A comparison of these structures reveals a relationship between the positions of the Tyr and Tic side chains and the activity of the peptide ligand. In TIPP (Tyr-Tic-Phe-Phe), a highly δ selective antagonist, the distance between these side chains is 5.5Å; in the agonist D-TIPP (Tyr-D-Tic-Phe-Phe) the distance between these side chains is approximately 6.5Å. Shorter ring-ring distances are associated with a conformation of enkephalin thought to re­present that of an antagonist, while longer ring-ring distances are associated with a conformation which is thought to be required for agonist activity.


MS05.01.04 CONFORMATIONAL CHANGES OF SMALL MOLECULES BINDING TO PROTEINS — COMPARISON OF CSD AND PDB STRUCTURES. Marc C. Nicklaus, Shaomeng Wang, John S. Driscoll, and George W. A. Milne; Laboratory of Medicinal Chemistry, Division of Basic Sciences, National Cancer Institute, National Institutes of Health, Bldg. 37, Rm. 5B29, 37 Con­vent Drive, Bethesda, MD 20892-4255, USA.

Flexible molecules change their conformation upon binding to a protein. This was shown by the analysis of small molecules whose structures have been determined by x-ray crystallography of both the pure compound and the compound bound to a protein. Thirty-three compounds present both in the Cambridge Structural Database and the Brookhaven Protein Data Bank were analyzed, and both were compared with the global energy minimum conformation in vacuum, computed by molecular mechanics force fields calculations. It was found that the conformation bound to the protein differs from that in the crystal structure and also from that of the global energy minimum, and the degree of deformation depends upon the number of freely rotatable bonds in the molecule. Four rotatable bonds ap­peared to be a limit beyond which no great similarities can generally be expected between the crystal, protein-bound, and vacuum confor­mations. Analysis of the conformational energies of the flexible molecules showed that, for most of those compounds, both the crystal and the protein-bound conformations are energetically well above the vacuum global minimum, and, in many cases, not even in any local energy minimum. Semiempirical calculations performed for a select number of structures, using both the AM1 and PM3 hamiltonians, confirmed these results. The number of ligand atoms forming hydrogen bonds was found to be correlated with the energy available for deformation of the ligand. The accuracy of the deter­mination of the conformation of protein-bound small molecules is discussed in the context of the resolution of the crystallographic struc­tures. These findings are discussed as to their impact upon contemp­orary methods of drug design.