COMPUTER PREDICTIONS OF GLYCOSPHINGOLIPID CONFORMATION

C.H. Wynn
Glycosphingolipid Research Group
Department of Biochemistry & Molecular Biology
School of Biological Sciences
University of Manchester
Manchester, M13 9PT
U.K.

Introduction

It is widely recognised that the interaction between macromolecules relies for its specificity on the complementarity of those molecules. For example, the interaction of enzyme with substrate or nucleic acid with protein depend on a variety of non-covalent forces such as hydrogen bonding, electrostatic interaction etc. The role of oligosaccharides in recognition phenomena, such as cell-cell interaction and receptor-ligand binding, has received considerable attention and it is apparent that such phenomena will depend on the interaction of complementary structures. Gangliosides, with their special roles in binding specific ligands such as toxins, hormones and growth factors (see 1) and in cell transformation and the development of malignancy (see 2), would seem to provide an example of the interaction of glycolipids with other molecules and, as such, a suitable model for the study of the nature of these interactions.

A variety of physical techniques have been used in the elucidation of the structure and linkages of gangliosides and other glycosphingolipids. Thus mass spectrometry in conjunction with direct probes (3), negative ion fast atom bombardment (4) or gas chromatography (5) have all contributed to our knowledge of the structures of these glycolipids. However, the absolute conformation of these molecules is a more intractable problem. The direct approach of X-ray crystallography commends itself but the application of this technique is limited to those substances, such as galactosyl-ceramide, where crystalline derivatives are available. Limited information has been obtained by the use of nuclear magnetic resonance spectrometry (6,7,8,9,10) but the interpretation of such spectra in specific conformational terms is often difficult and ambiguous.

Computational methods offer an alternative approach to the study of molecular conformations. The potential energy of a molecule is taken as the summation of the interaction energies of all possible pairs of atomic centres,
these interaction energies being made up of van der Waals' repulsion and attraction forces and electrostatic interactions between partial charges on the atoms. The parameters of these interactive forces have been obtained by comparison with experimental data (11,12,13). The relative weighting of the forces has varied from author to author but the 9-6-1 potential functions described by Hagler et al. (14) and Platt & Robson (15) are most commonly used. Refinement of the classical atom-centred approach, by inclusion of localised molecular orbitals representing lone pair and \( \pi \)-type orbitals associated with certain core atoms in the empirical energy calculations (orbital force field description, (6), has improved the molecular description. In 1965, Nelder & Mead (17) introduced the SIMPLEX procedure for the minimisation of the empirical potential energy of the whole molecule as a function of its conformation and this procedure has been extended by the addition of the GLOBEX routine by Robson et al. (18) in order to ensure that the minima located were of the deep meta-stable type rather than local, kinetically, facile, minima. In this way alternative conformers of similar energy can be detected and the search for new minima terminated when no new minima are found within the simulation time and the simplex points converge to within 0.05 kcal/mole. A review of the application of such methods to the prediction of protein folding has recently been published (19).

The computational prediction of the conformation of oligosaccharides and glycosphingolipids offers exciting challenges and presents several problems. The possibility of studying the effect of minor variations in structure on the overall conformation of the molecule could well be a useful tool in the elucidation of the antigenicity of blood group substances, histocompatibility antigens and a variety of growth and development factors. Similarly the use of such techniques in examination of receptor specificity would be valuable. However, it is not obvious that the parameters derived from model compounds for the study of proteins and peptides will be applicable to these other molecules, although, since these parameters concern the interaction of atomic centres, if the same centres are present, the same parameters should apply. The other major problem to be tackled is the role of solvent in the determination of conformation. This is particularly difficult in the case of glycosphingolipids, where the molecule is orientated at the lipid-aqueous interface in membranes and thus subjected to different solvents at different regions of the molecule. Throughout the studies described here the role of the solvent has been neglected since the complex nature of the environment and computational time limitations preclude