JOURNAL OF
MEDICINAL
CHEMISTRY

Volume 39, Number 1 January 5, 1996

Guest Editorial

The View from Inside the Receptor

Over the past five years, we have witnessed a new era in medicinal chemistry, arising from the application of molecular biology to the drug discovery process. There is a synergy that comes from viewing the receptor−ligand interaction from the perspective of the receptor, using molecular biological approaches in addition to the classical pharmacophore approach, in which the binding pocket is viewed from the perspective of the ligand. In the G protein coupled receptor field, molecular cloning has revealed substantial structural similarity among the receptor proteins, despite the wide diversity of their ligands. Generic models of G protein coupled receptors as membrane-spanning helical bundles have been built on the basis of the electron diffraction structures of bacteriorhodopsin and rhodopsin. To identify specific molecular interactions between ligands and receptors, receptor mutagenesis has been combined with modification of the ligand in an approach that may be thought of as two-dimensional mutagenesis. By examining the additivity of the effects of modifying functional groups on the ligand (using organic chemistry) and substitution of amino acid side chains on the recptor (using molecular biology), this two-dimensional approach allows the identification of specific interactions between the receptor and the ligand. The information from such experiments can then be applied to the receptor model to dock the ligand in the binding pocket and the orientation of the receptor helices adjusted to reflect the experimental data. The refined model will suggest other potential receptor−ligand interactions, which can serve as targets for medicinal chemistry in an iterative process to optimize binding interactions.

At its limit, this combination of medicinal chemistry and molecular biology can provide a low-resolution sketch of the interactions that dock the ligand in the receptor binding pocket. In the absence of high-resolution structural data, the models derived from two-dimensional mutagenesis provide insights into the receptor binding site that can be useful in the drug discovery process. Although the bound conformation of the ligand is not known, these experiments place limits on the possible configuration of the residues that comprise the receptor binding pocket: the orientation of these residues is constrained by the interatomic distances within the potential conformers of the ligand. These constraints place limits on the flexibility of the model and allow it to be used to make reasonable predictions about other potential binding interactions. In the absence of higher resolution structural information, such a model can be used to highlight residues near the binding site that can be exploited chemically to enhance the potency or specificity of the receptor−ligand interaction. In addition, differential effects of receptor mutations on different structural classes of receptor antagonists can identify points of overlap between the ligands, helping to refine the models of the pharmacophores themselves. It can be expected that the synergy between medicinal chemistry and molecular biology will hasten our progress toward the design of specific drugs to activate or inhibit these receptors.

Catherine D. Strader
Schering-Plough Research Institute

JM961181B

0022-2623/96/1839-0001$12.00/0