GPCR 3D modeling

Frank U. Axe

INTRODUCTION

G-protein-coupled receptors (GPCRs) are a superfamily of membrane proteins that provide cells with the ability to communicate with each other and their environment.[1,2] The core feature of these proteins is their seven transmembrane helices (7TM) that form a bundle located in the cell membrane (Figure 16.1). The seven helices are linked together by three extracellular loops (ECLs) and three intracellular loops (ICLs) and also include N- and C-terminal regions. This 7TM region is responsible for receiving a wide range of signals from small-molecule amines, peptides, proteins, small odorant and taste molecules, and light, which either bind in the interior of the 7TM bundle or to its extracellular surface or interact with chromophores located in its interior. These external signals trigger the coupling of the ICLs (in particular ICL5) with the heterotrimeric G-protein transducin, which in turn initiates a cascade of signaling events that lead to proliferation, differentiation, development, cell survival, angiogenesis, and hypertrophy.[1,2] In light of these facts it is not surprising to find that GPCRs are implicated as targets in a wide range of indications, including heart disease, allergies, depression, mental illness, cognition, and hypertension.[1–3]

The estimated number of GPCRs in humans is ~1,000 members or ~1% of the genome. There are five major classes of GPCRs that are defined by their sequence homology and the type of endogenous ligand.[1,2] The most important of these classes are A, B, and C. GPCRs are dysfunctional or dysregulated in many diseases making them the target of drug therapies.

Many of today's approved drugs target GPCRs and account for somewhere between 30 and 40% of the revenues from pharmaceutical sales.[3] This amounts to over (U.S.)$23.5 billion in sales annually.[3] Many of the well-known blockbuster drugs in use today like Zyrtec, Claritin, Singulair, and Risperdal target GPCRs.[3] So it is clear that many of the future drug treatments of existing and new diseases will involve GPCRs as targets for those therapies. As a result there is an ever-growing need to streamline the discovery process while leveraging all available resources to bring these new drug therapies to market.

Structure-based drug design is an integral part of the drug discovery process today and has played an essential role in the discovery of new pharmaceutical medicines.[4–7] In the past modeling of GPCR-based therapeutics more often than not involved traditional approaches like 2D searches (similarity, substructure),[6] quantitative structure activity relationships (QSAR),[6] pharmacophore,[8] and shape[9] analysis due to the absence of experimental structures of compounds bound to GPCRs. These methods can pinpoint new compound series or identify essential features for recognition by the receptor; however, they cannot predict outside the range of the probe or training set of molecule(s)[4] used in the analysis. Three dimensional (3D) modeling involving the target can enable the identification and refinement of leads without the necessity of a large set of active and inactive compounds.[5–7]

Since the year 2000 three new crystal structures of GPCRs have been published.[10–14] These structures have helped advance the state of the art of 3D modeling of GPCRs. This chapter reviews these new advances as well as the past literature on 3D modeling of GPCR drug interactions, including the current experimental structural information, techniques for building GPCR models, docking and virtual screening methods, and molecular dynamics studies. In addition future directions in 3D GPCR modeling are discussed.

CRYSTAL STRUCTURES

The experimental structural characterization of the 7TM bundle has proved elusive for several reasons, including conformational flexibility, purity, and solubility.[10–14] Thus, there is a paucity of crystal structures available for drug design work, especially when compared to what is available for enzyme targets. An essential ingredient to any target-based drug discovery project is a crystal structure of the target or one that is homologous to the target of interest.[4,5] In 2000 the first complete crystal structure of the mammalian GPCR, bovine rhodopsin, was solved.[10,11]

Rhodopsin is a light-activated GPCR in which 11-*cis*-retinal acts as a chromophore absorbing light, causing it to change conformation in the binding pocket and triggering a conformational change of the 7TM region. This initial