Molecular dynamics simulations of the β_2-adrenergic receptor in complex with a peptide derived from the Gα subunit of the heterotrimeric G_s-protein

Angela Götz[1], Peter Gmeiner[1], Tim Clark[2], Harald Lanig[2]

[1] *Department of Chemistry and Pharmacy, Emil Fischer Center, Friedrich Alexander University, Schuhstrasse 19, 91052 Erlangen.*

[2] *Department of Chemistry and Pharmacy, Computer Chemistry Center, Friedrich Alexander University,Nägelsbachstrasse 25, 91052 Erlangen.*

The β_2-adrenergic receptor is a member of the large family of G-protein coupled receptors (GPCRs). It belongs to the subfamily of rhodopsin-like receptors. Ligand binding to the transmembrane domain leads to conformational changes within the receptor and to activation of intracellular G-proteins.

In 2007, the β_2-adrenergic receptor was crystallized in its inactive conformation and the structure was widely-used for drug design studies. One year later, opsin was crystallized in its G-protein-interacting conformation. It was stabilized by an 11 amino acid synthetic peptide derived from the C-terminus of the Gα subunit of the G_t-protein interacting with the cytoplasmic part of the seven transmembrane (TM) helices.

The aim of our studies was to construct a receptor-peptide complex derived from the crystal structure of the β_2-adrenergic receptor and the C-terminus of the Gα subunit of the G_s-protein. Following, the impact of the C-terminal end of Gα on the structure of the ligand binding site and the interactions between receptor and the synthetic agonist Isoprenaline should be investigated.

By applying molecular dynamics simulations, the cytoplasmic half of TM6 of the β_2-adrenergic receptor was shifted outwards of the helical bundle by 6-7 Å to accommodate the C-terminal end of $G_s\alpha$ in the cytoplasmic part of the receptor as observed in the crystal structure of opsin. Following, the peptide-receptor complex as well as the original crystal structure of the β_2-adrenergic receptor were subjected to molecular dynamics simulations in a DOPC membrane. The simulations in both systems were carried out in presence and absence of Isoprenaline.

Although the peptide, interacting with the cytoplasmic part of the receptor, is not in close proximity to the ligand binding site, it significantly affects the structure of the binding pocket. Hydrogen bond patterns within the receptor and between receptor and ligand as well as root mean square deviation and fluctuation data are used to characterize the binding crevice. In addition, the binding site is divided into three different layers parallel to the membrane orientation. For each layer the helix-helix distances were calculated to monitor in detail changes in the structure of the binding pocket.

In this presentation, the results of the analyses will be discussed to elucidate the influence of the peptide on structure and dynamics of the ligand binding site.