CALIFORNIA STATE SCIENCE FAIR
2014 PROJECT SUMMARY

Name(s)

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Project Number

S0522

Project Title

3D Structure of DP Prostaglandin G-protein Coupled Receptor Bound to Selective Antagonists from GEnSeMBLE Predictions

Abstract

Objectives/Goals

G-protein coupled receptors are heptahelical transmembrane receptors that convert an extracellular signal to an intracellular response. They are implicated in multiple physiological functions and function as an important therapeutic target for diseases such as cancer to Parkinson's disease. Prostaglandins play a critical physiological role in both cardiovascular and immune systems, acting through its interactions with ten prostanoid G-protein coupled receptors (GPCRs). These receptors are important therapeutic targets, but lack of knowledge of 3D structures for the prostaglandin GPCRs hampers the use of structure based drug design methods to develop medications to specific receptors. Among these, the DP receptor is of interest because it has unique character and physiological properties.

Methods/Materials

Two methods were used for structural prediction. First, I used a modified-homology algorithm where the initial structure was generated based on the dopamine homology template due to sequence similarity. Two, I used the de-novo method, which individually optimizes the helices. Each template was heavily sampled along multiple angles, where lowest energy structures were evaluated for antagonist docking. Further, molecular dynamics was implemented to study how the receptor and its interactions relax in the membrane with the ligand.

Results

I was able to accurately predict the DP Prostaglandin structure. My results showed that the antagonist binds vertically in the 1-2-7 binding pocket interacting strongly with residues Arg 310 and Lys 76. This is consistent with earlier predictions and available experimental data. Additionally, my results can explain find that DP does not have the 3-6 ionic lock common to Class A GPCRs. Further, I can explain DP ligand subtype selectivity to PGD2 through DP structural features. Additionally, we found the receptor is able to relax and most interactions have stability through molecular dynamics.

Conclusions/Discussion

I have reported the predicted structure for the DP Prostaglandin receptor bound to selective antagonists. Through my research, we have an understanding of how the ligand interacts in the binding pocket. Also, we can understand how to build future therapeutics based on virtual ligand screening. Also, the structure chosen has both experimental and computational validation.

Summary Statement

My project computationally predicted the structure of a specific type of transmembrane receptors. Through prediction, we can now design tailored drugs to target these receptors and change the biochemical processing of multiple diseases.

Help Received

Dr. Goddard, Dr. Abrol, and Dr. Kim provided guidance throughout project; Mrs. Fallon provided many valuable insights and helped on presentation; Parents and sister provided encouragement