Introduction

G protein-coupled receptors (GPCRs) are the largest family of integral membrane proteins coded by the human genome. GPCRs are important for signal transduction with the general structural characteristic of a plasma membrane receptor with seven transmembrane segments (Figure 1). One example of a GPCR targeted by pharmaceutical companies is the β2-adrenergic receptor. Adrenergic receptors are found throughout the body and are triggered by the hormone epinephrine (also known as adrenaline, hence the name adrenergic). When epinephrine binds to the receptors, it causes a slight conformational change within the receptor. This change then triggers activation of a G-protein, which induces a response within the cell (for example, muscle contraction). When this signal transduction event functions normally in the body, it helps regulate heart rate and blood pressure and is important for the “fight or flight” response. Beta blockers are medically used to bind to adrenergic receptors, manipulating the hormone’s concentration. We have used rapid prototyping technology to model the interaction of the human β2-adrenergic receptor with the beta blocker, carazolol. By modeling the β2-adrenergic receptor, we hope to better understand GPCRs as well as understand the mechanism of hormone/drug binding, which will aid in developing better drug treatments.

Mechanism of the β adrenergic receptor: an example of GPCR signal transduction

1. Epinephrine binds to its specific receptor.

2. The occupied receptor causes replacement of the GDP bound to Gs by GTP, activating Gs transferred to the α-subunit.

3. Gs (α-subunit) moves to adenyl cyclase and activates it.

4. Adenylyl cyclase catalyzes the formation of cAMP.

5. cAMP activates PKA.

6. Phosphorylation of cellular proteins by PKA causes the cellular response to epinephrine.

7. cAMP is degraded, reversing the activation of PKA.

A conserved structure and mechanism

Figure 4. Overlay of bovine rhodopsin (cyan) and the human β2-adrenergic receptor (orange)

Figure 4 above demonstrates how conserved the structure, and hence the mechanism, of signal transduction using GPCRs really is. Rhodopsin, one of the most thoroughly studied GPCRs, binds retinal and is needed for vision. The two proteins’ active sites line up almost perfectly three dimensionally, even though the two proteins have seemingly completely different purposes.

A Pharmaceutical Target

Figure 5. β2-adrenergic receptor bound to the beta blocker drug carazolol (orange)

Many human diseases, such as diabetes and hypertension (high blood pressure) are linked to GPCRs. Determining the structure of GPCRs such as the β2-adrenergic receptor will lead to the development of more effective drug treatments. We have modeled the interaction between one such drug-GPCR interaction.

References
