µ-Opioid Receptors: No Pain, Addiction Gain?

Are You Hero-in or Out?

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Introduction:

G protein-coupled µ-opioid receptors play an important role in pain signaling throughout the body. Heroin, morphine, and other opiates target the µ-opioid receptor for pain killing purposes. Chemists are seeking to develop drugs that eliminate physiological side effects such as tolerance, dependence, and addiction. The discovery of such molecules will revolutionize pain treatment.

Figure 1:
Three views of our model of the µ-opioid receptor, the active site and side views produced through the use of Jmol imaging software. PDB: 4DKL

Process of Science:

✧ When the morphinan ligand ß-FNA binds deeply into the pocket of the µ-opioid receptor, the protein's structural alterations closely resemble conformations of the receptor after binding with an agonist. The amino acids that interact closely with ß-FNA identify the residues most likely to interact with analgesic opiates in the receptor, and those discovered in nearest proximity to the ligand during experimentation are the ones highlighted on the model (Fig. 1). These residues provide information about the kind and shape of agonists that may be used in order to obtain optimal analgesic properties.

✧ Oligomerization of the µ-opioid receptor allows insight to the manner in which agonists bind to the receptor with respect to its structure. Formation of a dimer (or simply an intimate interaction between two receptors in the membrane) alters the structure of the protein's binding site and may affect downstream cellular results of agonist binding. In the cell membrane, µ-opioid receptors work in concert with δ-opioid receptors. δ-opioid receptors relate more to the addiction and tolerance aspects of opiate binding, making it a focus to find a drug that acts as an agonist for the µ receptors and an antagonist for δ receptors. A receptor and drug work together to form the ideal site, structuring the receptor to produce various effects in the cell. This knowledge is essential to understanding ways in which opioid receptors function for analgesic purposes in the body.

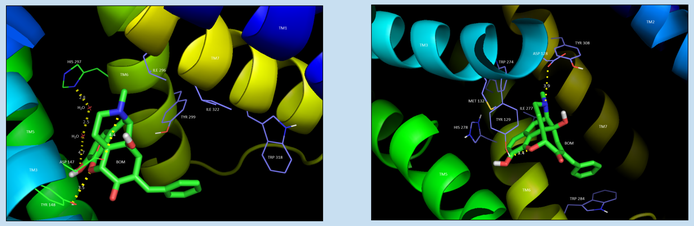

Figure 4:
Docking simulation produced through computation for µ and δ respectively.

Molecular Story:

✧ Opiate drugs mimic the natural pain killing endorphins produced by the brain in order to provide euphoria and pain killing properties. Many produce detrimental side-effects such as drug tolerance, addiction, dependency, respiratory problems, and constipation. Our model is a physical representation of a µ-opioid receptor, a member of the G protein-coupled receptors (GPCRs) family of molecules, which takes in opiates such as heroin and morphine. The structure and function of GPCRs are illustrated in Fig. 2.

✧ The µ-opioid receptor receives opiates and transmits messages to produce more pain killing substances. As a ligand binds within its large active site, the receptor activates a phosphorylation cascade in which inhibitory G proteins and other molecules generate cellular responses. The large binding pocket also allows for differential specificity of ligands and reversible reactions. For example, the molecule naloxone acts as an antagonist for the receptor and counters opioid overdose effects. The µ-opioid receptor holds the key to developing an ideal analgesic drug.

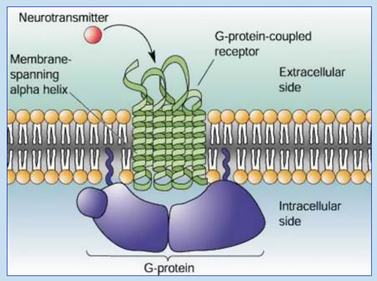

Figure 2:
A representative G protein-coupled receptor.

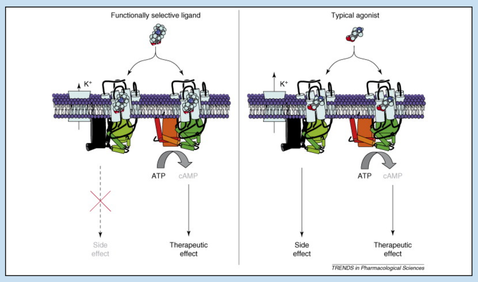

Figure 3:
The ideal molecule being pursued by our mentor.

✧ Dr. Chris Cunningham is developing different compounds to meet optimal criteria. Through his research, he has confirmed negative side effects are produced by arrestins, activated by the closely related δ-opioid receptor. As the pathway for the µ-opioid receptor leads to the intended pain killing properties, the δ-opioid produces more negative consequences. Dr. Cunningham pursues a molecule that will serve as an agonist for the µ-opioid receptor and an antagonist for the δ-opioid receptor, visualized by Fig. 3.

✧ We are modeling the µ-opioid receptor to answer questions about the structure of the active site where a compound would bind and function as an agonist. Significant limitations to the rigid model, however, include a lack of understanding of dynamic interactions in this receptor's active site and with other molecules. With this in mind, future models must be made to incorporate such characteristics.

Summary:

The µ-opioid receptor may be integral to unlocking a future where the medicinal use of opiate drugs achieves analgesic properties without negative side effects. Our model facilitates an understanding of the deep active site and how ligand molecules may manipulate it. Through investigations done by Dr. Cunningham and other researchers, finding a compound that functions as an agonist for the µ-opioid receptor and an antagonist for the δ-opioid receptor may soon be possible. An ideal molecule that prevents development of tolerance and addiction has the potential to solve the growing opiate abuse epidemic and revolutionize methods of pain killing in the medical community.

Bibliography:

PDB ID: 4DKL
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Acknowledgments:
The Longmont High School SMART Team would like to thank… all the work our teachers have done to keep us on track.