SMART Teams 2014-2015 Research & Design Phase

Madison West High School SMART Team

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Understanding the μ-Opioid Receptor Protein Binding Site Interactions with Ligands

PDB: 4DKL

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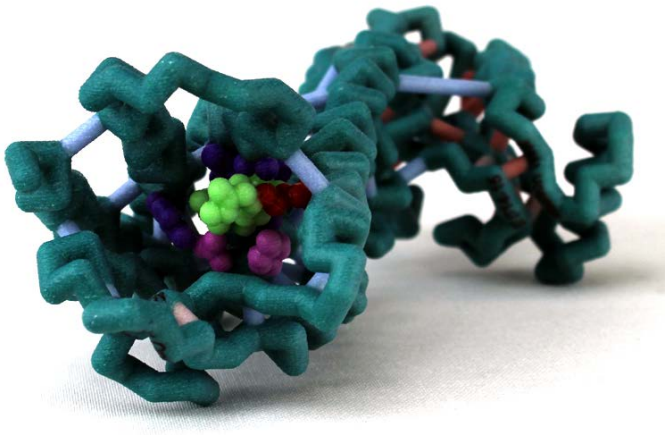
Abstract:



Opium and its derivatives have been used for centuries to treat severe acute or chronic pain by binding to opioid receptors in the body, causing beneficial effects of analgesic and harmful effects. Their addictiveness has led to several opiates becoming recreational drugs such as opium, morphine, and oxycodone. In addition, people build up tolerance to opiates decreasing their effectiveness over time. The main opioid receptors, μ-opioid receptors (μ-OR), are G-protein coupled receptors (GPCRs) that undergo conformational changes when a ligand such as opium or morphine binds to it, initiating a downstream effect that ultimately relieves pain. If scientists can understand the molecular interactions when drugs bind these receptors, they can begin to develop a drug that binds these receptors to relieve pain without signaling these negative side-effects. The crystal structure of the μ-opioid receptor bound to a morphinan antagonist reveals an unusually large binding pocket, allowing quick binding and many different molecules to bind with it. Residues around the binding site contact the bound molecule differently depending on the molecule. It is believed the triggering of these residues is what affects the person. The Madison West High School SMART (Students Modeling a Research Topic) Team modeled this bound G-protein coupled μ-OR by using Jmol protein modeling software and 3D printing technology to investigate the structure and function relationships of receptor interactions. An understanding of the binding site interactions of μ-OR, along with other structures that capture the active form of this bound receptor, will help researchers start to develop more useful drugs.

Specific Model Information:

beta-FNA: derivative of naltrexone, can function as a μ-receptor antagonist

M151, Y326, W293, I296, H297, V300: have hydrophobic interactions with beta-FNA

K233: covalently bonds with beta-FNA, the fact it covalently bonds signifies the importance of the interaction

D147: interacts with the amine moiety of the ligand and hydrogen bonds with Y326

Y148: polar interaction with beta-FNA

These amino acids help us understand the binding site where the drug interacts, and this is important because binding controls the activation of the opioid receptors.

- μ-Opioid Receptor: Teal
- Lysozyme (protein and struts): Rosy Brown

- Hydrogen bonds: Silver
- Disulfide bonds: Dodger Blue
- Struts: Light Sky Blue

- beta-FNA: Light Green
- K233: Maroon
- D147, Y148: pink
- M151, Y326, W293, I296, H297, V300: Purple

http://cbm.msoe.edu/smartTeams/

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