Opioids and The Mu Opioid Receptor

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Huang, W., Manglik, A., Venkatakrishnan, A., Laeremans, T., Feinberg, E., & Sanborn, A. et al. (2015). Structural insights into μ-opioid receptor activation. *Nature*, *524*(7565), 315-321. doi:10.1038/nature14886

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PDB Files:

6DDE *Koehl, A., Hu, H., Maeda, S., Manglik, A., Zhang, Y., & Kobilka, B. et al. (2018). Mu Opioid Receptor-Gi Protein Complex. doi:10.2210/pdb6dde/pdb*

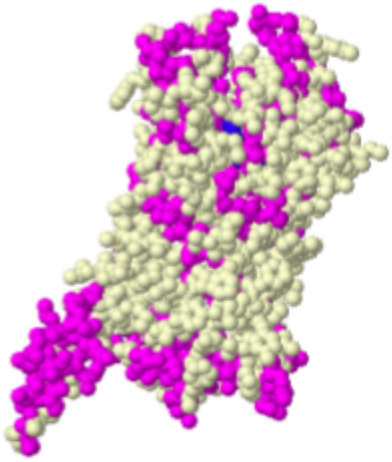
5C1M Huang, W., Manglik, A., Venkatakrishnan, A., Laeremans, T., Feinberg, E., & Sanborn, A. et al. (2015). Crystal structure of active mu-opioid receptor bound to the agonist BU72. doi:10.2210/pdb5c1m/pdb

4DKL Manglik, A., Kruse, A., Kobilka, T., Thian, F., Mathiesen, J., & Sunahara, R. et al. (2012). Crystal structure of the mu-opioid receptor bound to a morphinan antagonist. doi:10.2210/pdb4dkl/pdb

Mu and G-protein receptor complex

The mu opioid receptor (purple) is bound to the G-protein with three different subunits, or parts (alpha subunit - red, beta subunit -orange, gamma subunit yellow). The G-protein acts as a switch within the mu receptor. When there are no opioids bound to the mu-receptor the G-protein is dormant, but upon binding a series of events is initiated. The G-protein changes its connection from the GDP nucleotide to the GTP nucleotide. This transfer causes the nucleotide to break down, allowing for the different subunits to interact with other molecules and send signals to the brain, leading to the euphoric and anesthetic feelings caused by opioids.

Mu Opioid Receptor Complexed with G-Proteins



Mu Opioid Receptor with Morphine-like Agonist

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How the receptor releases or rids of the pain effect

Exogenous opioids are drugs that originate outside of the body, originally used for the purpose of killing pain. They effectively create an enhanced imitation of endogenous opioids, which are opioids that naturally occur inside the body. Many exogenous opioids bind to the mu opioid receptor. The morphine agonist (shown deeply seated in the ligand binding pocket in dark blue) binds with the mu-opioid receptor, causing conformational changes which initiate a cascade of effects within the cell. This cascade of effects is what eventually leads to the opioids dulling pain.

Mu Opioid Receptor bound to a Morphinan Antagonist

Binding but NOT Initiating

Like it can to agonists, the mu opioid receptor may also bind to a morphinan antagonist, ligands that DO NOT initiate a cascade of effect, but instead effectively block the receptor. Pictured here is a backbone representation of the mu opioid receptor shown in a light blue. The antagonist, shown in purple, can be seen embedded deep within the ligand bonding pocket. The key ligand bonding residues of the mu opioid receptor are shown in cyan. The binding of the antagonist to the mu opioid receptor fails to cause the same conformational change in the receptor that the agonist does. As a result, various physiological processes are not initiated.

Mu Opioid Receptor Bound to a Morphinian Antagonist