Whitefish Bay High School SMART Team

Katrina Burmeister, Evan Davis, Luke Dragseth, Austin Gent, Andrew Janssen, Stephen Koch, Mohammad Shaheer, Shadika Panta

Teachers: Paula Krukar, Katie Brown

Mentor: Christopher W. Cunningham, PH.D, Concordia University of Wisconsin

Inhibition of δ-Opioid Receptors

PDB: 4DKL

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Opioid addiction and abuse affects between 26 and 36 million people worldwide (Volkow, 2014), prompting researchers to try to design a drug that both has painkilling effects but does not create a dependency. Most opioid analgesics work through activation of mu opioid receptors (MOR). They naturally bind to opioid peptides, such as endomorphins 1 and 2, in order to regulate pain. Another important target is the delta opioid receptor (DOR). Inhibition of DOR has been shown to slow the development of addiction to MOR agonists in animal models of pain. DOR are proteins that transpermeate the cell membrane with seven alpha helices. Schiller and colleagues first reported an endomorphin analogue, DIPP-NH_2, that activates MOR and also inhibits DOR. DIPP-NH_2 is structurally similar to the natural endomorphins, so it can bind DOR through similar mechanisms. The DIPP-NH_2 interacts with the Met132, Tyr129, Val217, Ile277, and Trp284 on DOR. Moreover, one of the two methyl groups on DIPP-NH_2 engages Val281 and Ile277. Finally, a salt bridge forms between the DIPP-NH_2 N-terminus and Asp128, and this salt bridge is crucial for opioid receptor ligand recognition. The Whitefish Bay High School SMART team (Students Modeling a Research Topic) is modeling DOR using 3D printing technology. DIPP-NH_2 may be the basis of a non-addictive painkiller, which would be a significant advancement toward alleviating the major societal and financial problem of opioid addiction.

Secondary Citation: Volkow, Nora D. “America's Addiction to Opioids: Heroin and Prescription Drug Abuse.” *National Institute on Drug Abuse (NIDA)*, National Institute on Drug Abuse, 14 May 2014, www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse.