Closing the DOR on Opioid Addiction

Whitefish Bay High School SMART Team

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I. Introduction

Millions are affected by the addictive qualities of opioid painkillers (Volkow). Due to opioids' ability to treat pain, members of the medical community prescribe drugs such as morphine or oxycodone (OxyContin®). However, these drugs are extremely addictive and create an unhealthy dependency in the body, causing many patients to seek out the drug outside of a doctor's care. Because of this, a pain-killing drug that is non addictive is in high demand. A drug like this could open up a whole new world of possibilities to the medical community. Being able to treat the pain of patients without the risk of an addiction would bring much more comfort to the patients themselves. DIPP-NH_2 could very well be that drug that the medical community desperately needs by reducing the risk of opioid addiction.

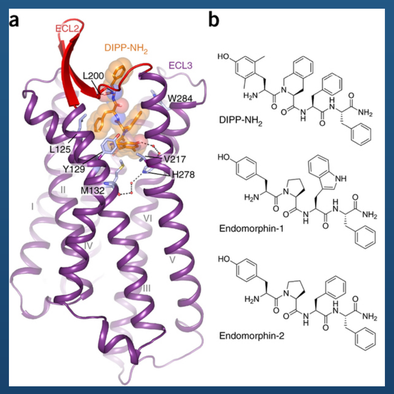

Figure 1: Comparison of the structure of endogenous endomorphins with DIPP-NH_2, and how DIPP-NH_2 attaches to DOR.

Fenalti, G., et. al.(2015)

II. The Science of DIPP-NH_2

Pain management in the brain is regulated by peptides binding to and activating protein receptors in the brain, such as the δ-opioid receptors (DORs) and μ-opioid receptors (MORs). The tetrapeptide analog DIPP-NH_2 works similarly, and is structurally similar to endogenous opioid peptides (Fig 2b). However, by replacing the proline found in endogenous peptides like endomorphin-2 with a Tic scaffold (1,2,3,4 tetrahydroisoquinoline-3-carboxylic acid), potent bifunctional compounds like DIPP-NH_2 can be created. DIPP is bifunctional in that it is both a MOR-agonist and a DOR-antagonist. The Tic side chain of DIPP-NH_2 resides in a hydrophobic area created by alpha helices IV and VII. The dimethyl residue of DIPP-NH_2 binds with amino acids Met132, Tyr129, Val217, Val281, Ile277, and Trp284 on the DOR. Also, the N-terminal amine of Dmt (2,6-dimethyltyrosine) connects to Asp128 via a salt bridge; this interaction is crucial for the recognition of opioid receptor ligands.

III. Structure of DOR

Figure 2: DIPP-NH2 bonded to DOR. Modeled in Jmol based on PDB file 4RWA. Printed by MSOE using Zcorp printer

Structural features of DOR highlighted in the model include alpha helices (chartreuse), beta sheets (red), hydrogen bonds (goldenrod), disulfide bond (yellow), Asp128 (orange), and the amino acids that serve as DIPP binding sites (hot pink). Struts, colored tan, are not actually part of the molecule but serve but were added for structural support.Asp128 is highlighted uniquely because it is important in opioid receptor ligand recognition. DIPP-NH_2 is located at the center and colored CPK.

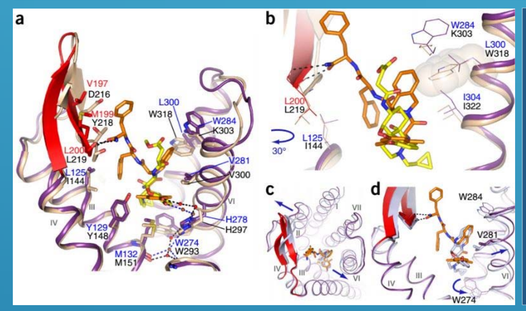

Figure 3: Diagram illustrating the structural movements that occur within the DOR to allow DIPP-NH2 to bind successfully.

Fenalti, G., et. al.(2015)

IV. Relevant Receptors

δ-opioid receptors (DOR) are endogenous opioid receptors that appear to contribute to forming memories associated with addictions, yet they do not block much pain. μ opioid receptor (MOR) agonists are more useful for blocking pain signals than DOR agonists, but can generate rewarding effects. Thus, the optimal analgesic lacking addictive properties would be a MOR agonist that also acts as a DOR antagonist. Ideally, this substance would also not activate κ-opioid receptors (KOR), since KOR activation can cause hallucinations. This poses a real challenge to medicinal chemists. The peptide, DIPP-NH_2 was one of the first agents to meet these criteria, making it a prized research tool.

V. Current DIPP-velopments

The peptidomimedic compounds 14a and 14j designed by Mosberg, et al. are comparable to DIPP-NH_2 in that they are structurally similar, activate and inhibit the same receptors, and bond to the same amino acid residues on the protein receptors. 14a and 14j were developed to have improved stability and balance over DIPP-NH_2 in terms of MOR and DOR binding affinities, while simultaneously avoiding activation of the κ-opioid receptor (KOR), which can cause hallucinogenic effects. Figure 4 illustrates how 14a and 14j bind to DOR.

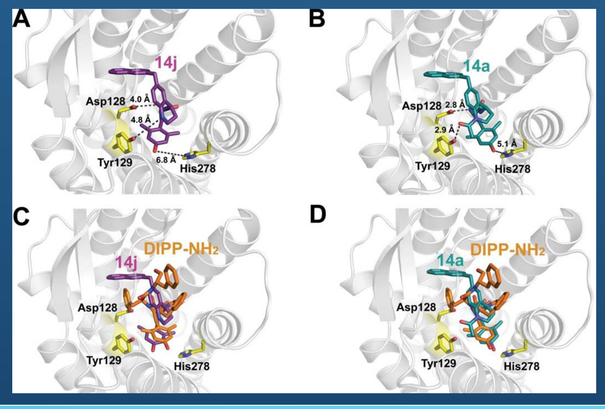

Figure 4: Rendering of peptidomimetic compounds 14j and 14a in the inactive state of DOR (DORi). Upon examination of panels A and B, one can observe that substance 14a has closer contacts than 14j in ion/ion bonding with Asp128, and hydrogen bonding with Tyr129 and His278. This contact results in 14a having 50-times higher DORi affinity than 14j. C and D illustrate how the two compounds occupy a space similar to that of DIPP-NH_2

Harland, A. A. et al. (2015)

VI. Summary

Due to the addictive properties of widely-used opioid analgesics, the need has arisen to synthesize non-addictive painkillers. Scientific findings have shown that in order to synthesize a drug that has both painkilling and non-addictive properties, it is best for the compound to be a MOR-agonist and a DOR-antagonist. DIPP-NH_2 fulfills these criteria and is one of the most widely-researched compounds in this field of study as it was the first bifunctional molecule found. Development of a MOR-agonist/DOR-antagonist may lead to safer treatments due to their lack of the addictive qualities found in current painkillers.

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