

'I Wanna New Drug'

Manipulating Kappa Opioid Receptor Ligands to Induce A Pain Relieving Response

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I. Abstract

Dangerous painkillers may cause serious problems for those who fall into drugs' addictive trap, such as former NFL quarterback Brett Favre. The addictiveness of painkillers such as OxyContin and Vicodin is largely attributed to the response they trigger in proteins such as mu opioid receptors (MOPs). This receptor activates cellular signaling pathways responsible for dulling pain; however, the protein also has the ability to stimulate cellular signaling pathways that makes MOP-based painkillers rewarding. An alternate target that alleviates pain but does not produce reward is the kappa opioid receptor (KOP). Unfortunately, many KOP agonists also activate signaling pathways that produce hallucinogenic effects. To investigate the changes that occur when KOP binds to different ligands, the Divine Savior Holy Angels SMART (Students Modeling A Research Topic) Team has used 3D printing technology to model the active site of the KOP with salvinorin A, to see how the induced fit changes the signal transduction pathways in a neuron. Manipulating receptor proteins like the KOP to inhibit pain pathways without the addictive effect of MOP-targeting painkillers would be a breakthrough in chronic pain management. Computer-aided drug design helps streamline the development of KOP ligands that activate this receptor in ways that result in less hallucinogenic effects.

II. Introduction

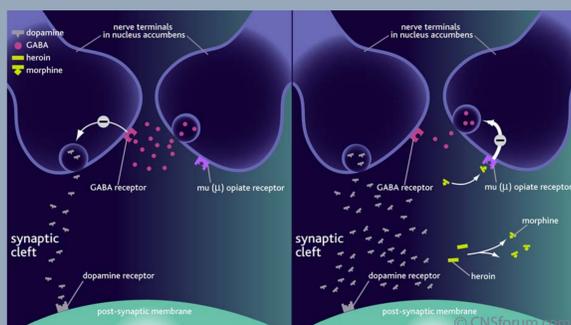


Figure 1. Drugs bind to the opiate receptor causing a feeling of pain relief. This, however, also has adverse effects as the body becomes dependent on the drug. Salvinorin A and the KOP receptors function similarly in this way.

MOP, KOP, and the delta opioid (DOP) receptors are the three main opioid receptors naturally targeted by most opioid agonists, including synthetic opioids such as oxycodone, and opioid signaling molecules such as endorphins that are naturally synthesized by the body. Agonists of the KOP receptor, such as salvinorin A, are effective at reducing pain without activating the reward pathway that leads to dependence. However, the KOP receptor is associated with its own set of adverse effects including dysphoria and hallucination. Understanding how agents like salvinorin A interact with the KOP receptor will aid in our development of analgesics lacking dependence that do not cause hallucinations.

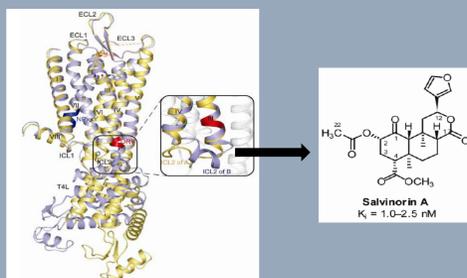


Figure 2. From left to right: A ribbon model of the KOP receptor protein, and the chemical makeup of the agonist, Salvinorin A.

III. Anatomy of the Kappa Opioid Receptor

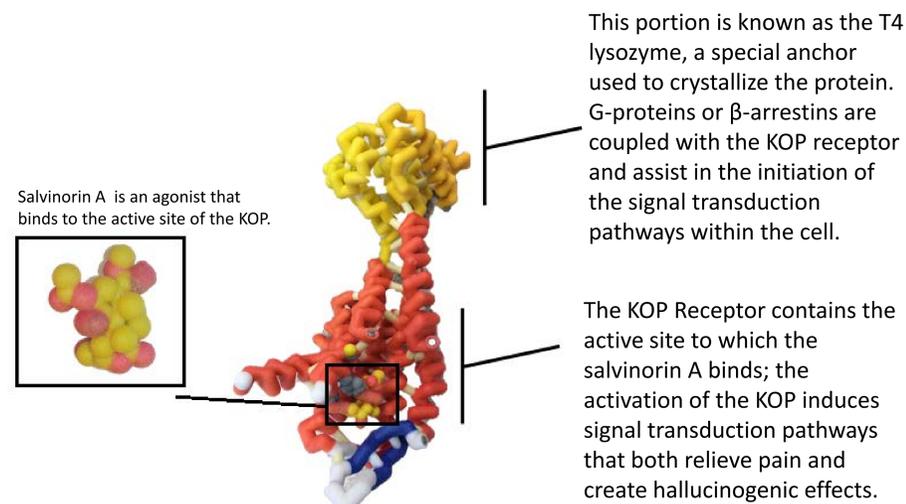


Figure 3. The 3-D printed model of the KOP Receptor

IV. Signal pathway of Kappa Opioid Receptor

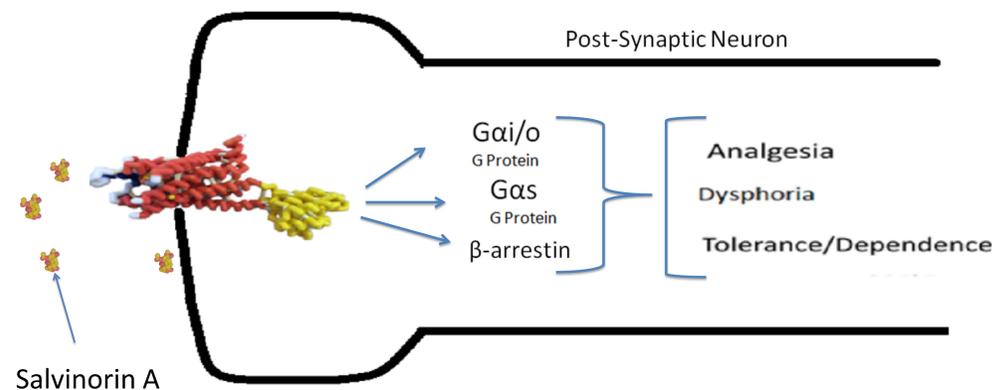


Figure 4. When the agonist, Salvinorin A, binds to the active site of the KOP receptor protein, the G-coupled receptor is activated. The activation of the proteins stimulates three major signal transduction pathways. $G_{\alpha i/o}$, $G_{\alpha s}$, and β -arrestin are three of several proteins that are known to interact with the KOP receptor although there is no definite knowledge of which protein produces each response.

Cells communicate through the binding of ligands to the receptors on the cell membranes of specific cells. Multiple signaling pathways can result from the binding of a single ligand. Adverse side effects result from unexpected signals coming from the ligand; they can fix one problem while creating another.

V. Application of KOP Model to Drug Design

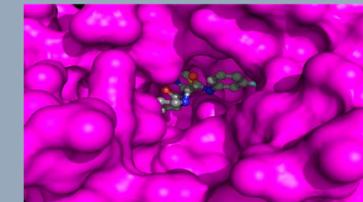


Figure 5: A representation of MCKK-17 in the KOP active site.

The table shown below shows various active compounds with their corresponding chemical structure and binding affinity values with given receptor proteins. The compound MCKK-17 shows the highest potency as an agonist for the KOP and therefore demonstrates a high affinity for that particular receptor. Salvinorin A has a similar structure to the compound MCKK-17 because Sal A have a very high affinity for the KOP as well.

Compound (Rank)	Structure	KOP	Ki (µM) DOP	MOP
MCKK-4 (97)		290 ± 210	640 ± 190	910 ± 840
MCKK-5 (111)		130 ± 81	180 ± 190	430 ± 140
MCKK-13 (347)		450 ± 27	300 ± 99	>10000
MCKK-17 (403)		17R: 2900 ± 960 17S: 120 ± 38	17R: 290 ± 320 17S: >10000	17R: 510 ± 640 17S: >10000

Table 1: The affinity of several different compounds to the KOP, MOP, and DOP receptors.

Table 1 shows the results of a virtual docking study reported recently.⁶ In the study, a virtual library of over 4.5 million compounds was screened based on compatibility with the KOP active site. Each compound bound to the active site at varying levels. The goal was to find the one that bound to the active site most closely to the way salvinorin A binds. The most potent compounds from the computerized screening of the compounds were purchased and tested *in vitro* for affinity and efficacy at KOP, MOP, and DOP receptors. The KOP receptor and MCKK-17 showed clear compatibility. Like salvinorin A, MCKK-17 was highly potent in only the KOP receptor and does not share structural similarities with the other antagonists that were purchased.

VI. Conclusion

The rise in opioid users and the potential for adverse side effects with the use of opioids has prompted researchers and pharmacologists alike to study the specific receptors in the body that opioids affect. In this regard, pharmacologists recognize the effectiveness of opioids in reducing or eliminating chronic pain in patients, but are searching for new ways to create drug compounds that effectively treat pain without adverse effects.

VII. References

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