K37 Study of the Mu-, Kappa-, and Delta-Opioid Receptor Models and the Kratom Alkaloids

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Learning Overview: After attending this presentation, attendees will better understand the interactions of kratom and its various alkaloids with the mu-, kappa-, and delta-opioid receptors.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by contributing to the understanding of complex interactions between substituents of specific kratom alkaloids with the mu-, kappa-, and delta-opioid receptors. Understanding these key interactions can help lead to improved knowledge of the effects these alkaloids produce.

Kratom, *Mitragyna speciosa*, is a plant indigenous to countries of southeast Asia and has traditionally been used for medicinal treatments.[1] However, the popularity of the drug has significantly increased recently due to its euphoric effects, leading it to being used as an alternative to illegal opioids. Several alkaloid compounds have been isolated from the leaves of the plant. The main alkaloids seen are the following five alkaloids: mitragynine, 7-hydroxymitragynine, speciociliatine, speciogynine, and paynantheine. Two alkaloids, mitragynine and 7-hydroxymitragynine, have exhibited high potencies and are potentially even more potent than morphine.[2] Previous studies have indicated that the main mediator of the psychoactive effects is the opioid receptor system, specifically the mu-, kappa, and delta-opioid receptors.[3] Agonistic activity has been seen by mitragynine and 7-hydroymitragynine at the mu-opioid receptor while antagonistic activity has been seen by all five of the above alkaloids at the kappa- and delta-opioid receptors. The highest binding affinities occur at the mu-opioid receptor and lesser affinities at the kappa- and delta-opioid receptors. Expanding concern of kratom has led to more research into its mechanism of binding with target receptors and how its growth of use impacts the forensic science and criminal justice community.

In this study, mu-, kappa-, and delta-opioid receptor models were used to establish the ligand-receptor interactions between the receptors and the constituents of specific kratom alkaloids. This was accomplished using Schrodinger's Maestro molecular modeling software. The major natural alkaloids of the plant were selected for this study because of their high abundances as well as their binding affinities. Maestro employs the technique known as molecular docking to study the binding of a ligand to the active site of a known 3D protein model. The docking of the ligands to proteins is used to determine the most accurate orientation of the ligand in the active site and the specific interactions that take place between the ligand and the protein. Maestro determines a "docking score" that is not the same as the experimental binding affinity but is related in terms of ranking the binding of the ligands to the receptor. Docking of the ligands to the receptors took place after both the alkaloid ligands and the opioid receptor models were prepped for docking and a grid of the active sites was generated. Data generated from each docking yielded information on the best poses/positions of the alkaloids for binding to the receptors, interactions between the ligands and receptors, and the estimated binding affinities.

The results of this study provide a better understanding of the interactions that take place between kratom alkaloids and the opioid receptors. Specific structural characteristics of the alkaloids studied were found to influence key residue interactions with the receptors. This study looked at structural characteristics, such as: length of the alkyl chain; presence or absence of function groups, including ketone, ester, and hydroxyl; and amine groups. Some residues were present consistently throughout the studies, including Asp147, Tyr148, and His297 in the mu-opioid receptor, Tyr129 in the delta opioid receptor, and Asp138 in the kappa opioid receptor. All these residues have been found to be important residues in activation of the opioid receptors.[4] The next step of this research will include comparing the docking studies with the different receptors to the known binding affinities to gain a better understanding of what is influencing the binding affinities and the adverse reactions of the kratom alkaloids. The results from this study will aid in the understanding of the influence specific structural characteristics have on the binding and pharmacology of these drugs. Future results from this study will lead to a new understanding of the effects kratom and its alkaloids have within the human body and help determine its potential for abuse.

Reference(s):

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