K40 Investigating the Binding of Fentanyl and Fentanyl Analogs to the Opioid Receptors

Marissa A. Teske, Olive Branch, MS 38654; Caroline Spencer, BS, Oxford, MS 38655; Pankaj Pandey, PhD, University of Mississippi, University, MS 38677; Robert J. Doerksen, PhD, University of Mississippi, University, MS 38677; Murrell Godfrey, PhD, University of Mississippi, University, MS 38677*

Learning Overview: After attending this presentation, attendees will better understand the interactions between fentanyl and its various analogs with the mu-, kappa-, and sigma-opioid receptors in the brain.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by contributing to the understanding of the interactions between fentanyl, fentanyl analogs and the mu-, kappa-, and sigma-opioid receptors, and of the specific interactions that are related to the adverse effects of these drugs.

Fentanyl was synthesized in 1960 by Dr. Paul Janssen of the Janssen Company to act as a rapid-acting analgesic that, unlike similar analgesics around that time, did not have negative cardiovascular effects.[1] Fentanyl overdoses were first reported around 1972 with subsequent increases in overdose cases reported as additional methods of administration became available.[1] From 1999 to 2011, the number of fatal opioid analgesic overdoses quadrupled and, for the year 2015, the death toll in the United States totaled 33,091.[2] The lacing of heroine with fentanyl by drug dealers in order to increase the client's opioid high is one major reason for this spike in overdose deaths. Fentanyl and its analogs are all agonists of the opioid receptors.[2] There are several physical effects of opioid binding at the μ-opioid receptor, including respiratory and central nervous system depression.[2] Fentanyl-related deaths are increasing rapidly, and more potent fentanyl analogs are found laced in heroin and cocaine every day. It is therefore imperative that scientists stay ahead of the illegal drug trade. One way this goal can be accomplished is by using cutting-edge technology to investigate ligand binding and molecular docking of illegal substances before they even enter the market.

This study examined the interactions that take place between fentanyl, and its analogs, and the opioid receptors they interact with in the body. The molecular modeling software, Maestro, was used to study these specific interactions. Fentanyl and its analogs were sketched and prepped for docking to the receptors using Maestro. The opioid receptors were chosen for this study from available, active-state crystal structures. The data from this study identified specific interactions that take place between these drugs and the binding site of corresponding opioid receptors. Key residue interactions included aromatic stacking interactions, hydrophobic interactions, polar interactions, and hydrogen bonding. These interactions corresponded to varying structural changes between fentanyl and its analogs. The interactions and structural changes were used to help better understand the potency and toxicity of fentanyl and fentanyl analogs. Future work will include using the results of this study to help predict potential new analogs of fentanyl before they appear on the drug market. Scientists and law enforcement will have advanced knowledge on various fentanyl-related substances to improve both detection and treatment of fatal overdose cases.

Reference(s):

1. Stanley, T.H. (2014). The Fentanyl Story. *The Journal of Pain, 15*(12), 1215-1226.
2. Armenian, P., Vo, K.T., Barr-Walker, J., and Lynch, K.L. (2017). Fentanyl, Fentanyl Analogs and Novel Synthetic Opioids: A Comprehensive Review. *Neuropharmacology*.

Fentanyl, Opioid Receptor, Molecular Modeling