RTI Prominent Publications Summary

Structure of the Human Kappa-Opioid Receptor in Complex with JDTic

Wu, H., Wacker, D., Mileni, M., Katritch, V., Han, G.W., Vardy, E., Liu, W., Thompson, A.A., Huang, X-P., **Carroll, F.I., Mascarella, S.W.**, et al. (2012) Structure of the human κ-opioid receptor in complex with JDTic. *Nature* 485 (7398): 327-332.

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The mechanism of interaction between opioid receptors and drugs in the central nervous system has been the goal for more than 60 years of research. An understanding of this interaction is necessary to the development of effective drugs for treating depression, anxiety, and addiction.

Opioid drug development has been hampered by the lack of any clear picture of the three-dimensional structure of any of the four opioid receptors. The determination of the structure of such membrane-bound receptors has been very elusive, and it depends on the discovery of ligands that bind tightly with the receptor to lock the structure into a stable conformation, which can be examined by X-ray crystallography. Although X-ray crystallographers had attempted to obtain useful crystals of opioid receptor proteins by combining with a very large number of known opioid drugs, these efforts had not yielded any useful pictures of an opioid receptor. However, the situation changed dramatically in 2012 when X-ray crystallographic studies were performed using JDTic, a kappa-opioid ligand developed at RTI International. Using JDTic, X-ray crystallographers at the Scripps Research Institute were able for the first time to obtain an accurate picture of a drug molecule bound to an opioid receptor. This high-resolution structural information, both of an opioid receptor itself and the details of the molecular interaction between an opioid drug and receptor, will provide invaluable guidance for the development of new treatments for depression, anxiety, and addiction.

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