Identification of Subtype-Selective Binding Sites in the Opioid Receptor Family

Gomes Antoniel A. S.[1,2,3,4], Guillot Benoît[4], Jelsch Christian[4], Giraldo Jesús[1,2,3]

[1]*Laboratory of Molecular Neuropharmacology and Bioinformatics, Unitat de Bioestadística and Institut de Neurociències, Universitat Autònoma de Barcelona, 08193, Bellaterra, Spain*

[2]*Unitat de Neurociència Traslacional, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí (I3PT), Institut de Neurociències, Universitat Autònoma de Barcelona, 08193, Bellaterra, Spain*

[3]*Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental, (CIBERSAM), 28029, Madrid, Spain*

[4]*CRM[2], CNRS UMR 7036, Faculté des Sciences et Technologies, Université de Lorraine, 54000, Nancy, France*

Abstract Text : The opioid receptor (OR) family is part of the class A G Protein-Coupled Receptors (GPCRs), comprising the mu (μOR), delta (δOR), kappa (κOR), and nociception (NOP) receptors.[1] Activating these receptors promotes pain relief, which includes acute, chronic, neuropathic, and inflammatory pain, among other effects.[2] The search for selective OR modulators can provide more effective analgesics with reduced unwanted effects.[3] Integrating structure-based approaches with binding kinetics can effectively identify potential selective druggable regions and determine ligand candidates for improved therapies.[4] In this study, we combined molecular dynamics simulations and metadynamics with charge density analyses to identify unique structural aspects of μOR, δOR, and κOR. We found distinct conformational dynamics between the receptors, with the κOR extracellular vestibule tending to form a lid that covers its orthosteric site. Furthermore, we investigated how morphinan-scaffold ligands with distinct pharmacological effects bind to OR orthosteric sites and extracellular vestibules, identifying intermediate ligand states. Moreover, we determined the role of orthosteric subpockets and extracellular loops in stabilizing ligand-bound states, shedding light on ligand selectivity. Our results provide a detailed description of the conformational dynamics and structure-based selectivity within the OR family from an energetic perspective. These regions (figure 1) can be rationally targeted for designing and developing functionally selective opioid modulators with improved pharmacological effects in pain treatment or other OR-related diseases.

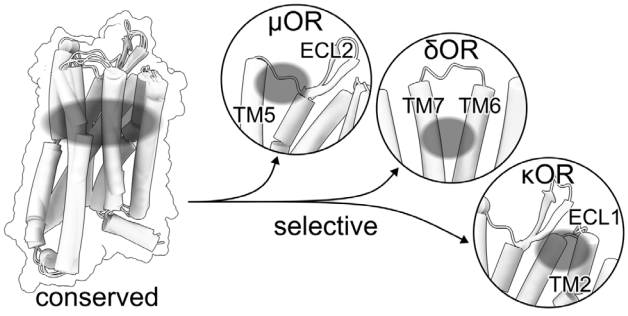

figure 1. Identification of conserved and binding sites in the Opioid Receptor family

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