THC

CBD

CBG

19ª Reunión Anual de la Sociedad Española de INVESTIGACIÓN SOBRE CANNABINOIDES

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STRUCTURAL INSIGHTS INTO THE βARRESTIN-CB_1 RECEPTOR INTERACTION: NMR AND CD STUDIES ON MODEL PEPTIDES

Morales P., Bruix M., Jiménez MA.

Departamento de Química-Física Biológica, Instituto de Química Física Rocasolano (IQFR-CSIC), Serrano 119, 28006-Madrid, Spain

Activation of the CB_1 receptor has been shown to induce different cellular signaling cascades through coupling to different effector proteins: G-protein ($G\alpha_{i/o}$) and β-arrestins (1 and 2). Numerous therapeutic applications have been demonstrated for CB_1 agonists including anti-emesis and appetite stimulation for AIDs patients, symptomatic relief of neuropathic pain and spinal cord injury, and antitumoral effects. However, psychoactive side effects limit the use of these agonists. In this scenario, the search for a biased ligand that can induce specific receptor activation profiles resulting in specific subsets of signaling pathways (biased signaling) has recently received a special attention in the cannabinoid field. This is due to the possibility of attaining different therapeutic effects and/or avoiding untoward effects while targeting the same receptor protein.

From a structural perspective, conformational changes in the receptor and rearrangements at the intracellular domain of the receptor that accompany ligand binding dictate the signaling pathways. The GPCR-binding interface for G proteins has been extensively studied whereas β-arrestin/GPCR complexes are poorly understood. In an effort to gain knowledge in this direction, we propose a biophysical approach to provide a mechanistic insight into the arrestin/CB_1 interaction.

For this purpose, we designed peptides that mimic the motifs involved in the interacting region: β-arrestinl finger loop and the transmembrane helix 7-helix 8 (TMH7-Hx8) elbow located at the intracellular side of the CB_1 receptor. Circular dichroism and NMR studies have been used to study the conformation of these peptides along with their interaction in aqueous solution, in the presence of trifluoroethanol, and using zwitterionic (dodecylphosphocholine) detergent micelles as membrane mimics.

The elucidation of specific conformational changes in the CB_1 receptor that result in distinct subsets of downstream signaling pathways through G-protein or β-arrestin may increase our understanding of these pathways promising receptor. This knowledge would enable the design of biased ligands to explore optimized therapeutic effects at the CB_1 receptor.

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