INTERACTION BETWEEN M2 MUSCARINIC RECEPTORS AND β-1 ARRESTIN IN GLIBLASTOMA CELL LINES: EFFECTS MEDIATED BY ORTHOSTERIC AND DUALSTERIC AGONISTS

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Topic & Theme selection

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Title

Abstract Body

Abstract body: Glioblastoma (GBM) is the most aggressive primary brain tumor in humans, characterized by the presence of stem cells, responsible for drug resistance and recurrence. For this reason, the identification of a new therapeutic target for GBM may be a promising challenge in tumor treatment. Many reports suggest that M2 muscarinic receptors (M2Rs) inhibit cell proliferation, survival and migration in several tumor types. Previous data demonstrated that the activation of M2R by orthosteric agonist Arecaidine-Propargyl-Ester (APE) and dualsteric agonist N8-Iper decreased cell proliferation and survival in GBM cells. Molecular docking using AutoDock4 and AutoDock Vina software was studied to evaluate the molecular interactions of the two ligands with M2R, identifying specific binding sites both on orthosteric and allosteric regions of the receptor. In particular, the N8-Iper orthosteric portion shares many interactions with the orthosteric agonist Iperoxo with a specific polar interaction in Ser107. In the allosteric region, N8-Iper shares some interactions with an allosteric modulator LY2119620. By cell transfection with two plasmid constructs overexpressing M2-Flag and β-Arrestin1-EGFP, we studied the localization of the two proteins observing a translocation of M2R from cytoplasm onto plasma membrane, and from nucleus to cytoplasm for β-Arrestin1. These results are also confirmed by western blot analysis. Interestingly, β-Arrestin1, upon chronic stimulation with M2 agonists, results significantly downregulated, suggesting that cholinergic stimulation may counteract the M2R internalization, prolonging the efficacy of the ligands, with a potential beneficial advantage in GBM therapy. Further experiments will be performed for a better characterization of the effects downstream the M2/β1-Arrestin1 pathway.

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Poster Group Code

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