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Structural conformational changes report biased agonism: The case of galanin receptors

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Statement of the Problem: G protein coupled receptors (GPCRs), also known as seven-transmembrane receptors are the largest family of cell-surface receptors that communicate extracellular stimuli to the cell interior. To date it has been widely accepted synthetic ligands targeting the same receptor can stabilize multiple active structural conformations having therefore differential signaling that eventually results in different physiological responses a phenomenon better known as biased agonism. However biased agonism might not only be restricted to synthetic ligands but also to endogenous ligands targeting the same receptor which may explain such a ligand redundancy, suggesting the existence of endogenous biased agonism as a physiological mechanism.

Methodology & Theoretical Orientation: The aim of this study was to establish a relationship between conformational changes in galanin receptors and their signaling properties in living cells. For that purpose, we developed a structural complementation assay based on NanoBit technology and a series of conformational fluorescein arsenical hairpin (FIAsH) bioluminescence resonance energy transfer (BRET) biosensors to monitor structural changes of β-arrestin 2 induced by binding with each galanin receptor.

Findings: Here we showed that galanin receptors impose different conformational signatures in β-arrestin, moreover structurally different ligands activating the same receptor imposed different conformations in β-arrestin 2 producing biased signaling.

Conclusion & Significance: Our data provide definite evidence that a receptor activated by structurally different ligands can adopt multiple active conformations. Moreover, this finding also demonstrates that functionally specific structural galanin receptor conformations can indeed be translated to downstream effectors producing a different physiological response.

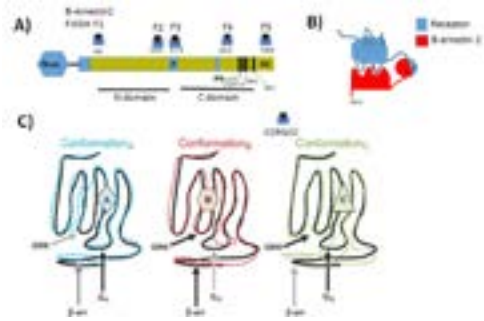

Figure: A) Five NLuc-ß-arrestin 2-FIASH BRET structural biosensors (F1-F5) were constructed by inserting the amino acid motif CCPGCC after amino acid residues 40, 140, 171 263 and 410 of ß-arrestin2. The location of each FIASH motif is shown in relation to the globular N and C domains of ß-arrestin2. B) Diagram of the structural complementation assay used to measure in real time binding between ß-arrestin2 and Galanin receptors. C) Schematic diagram depicting levels of conformational aberration produced in different areas of the receptor upon stabilization of receptor conformations by different agonists. Arrows depict various regions of interaction of the receptor with cytosolic proteins such as different G-proteins and ß-arrestin. It might be surmised that dissimilar conformations affect these various regions to varying degrees causing respective differences in effect for diverse coupling mechanisms.

Biography

Arfaxad Reyes Alcaraz has his expertise in structure and stability of G-protein coupled receptors and passion for improving and creating new drug discovery platforms that greatly contribute in the development of more selective drugs with minor side effects. His studies about biased agonism in galanin receptors helped to understand the relationship between conformational structure of the receptor and its corresponding physiological effect induced by a specific ligand. Recently, he and his co-workers were able to develop a highly selective agonist for galanin receptor 2 with anxiolytic effect *in vivo* which was the base to discover how different ligand structures induce different conformations on the structure of galanin receptors. His works greatly contribute to understand the relationship between structure and function of galanin receptors.

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