Autacoids

Kontoyianni, J Autacoids 2015, 5:1
http://dx.doi.org/10.4172/2161-0479.1000e130

Editorial Open access

G Protein Coupled Receptors: Druggability and Structural Aspects

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Rec date: May 11, 2015, **Acc date:** May 14, 2015, **Pub date:** May 16, 2015

G Protein Coupled Receptors

The 2012 Nobel in Chemistry was awarded to Robert Lefkowitz and Brian Kobilka for their scientific contributions in the inner-workings of G protein coupled receptor (GPCR) function. What culminated to this prestigious award was years of scientific endeavors by the above investigators and others towards understanding the structural basis of GPCR function. It is estimated 800 GPCRs are found in the human genome, which makes them one of the largest families in the proteome. Nevertheless, not all of them are potential drug targets. Specifically, 290 to 401 GPCRs [1] could be amenable to therapeutic intervention, with about 46 of them having been targeted to date. Thus, there is still a significant number of GPCRs that could be related to human diseases. However, while there is no skepticism regarding the value of GPCRs as drug targets, the question is whether an activated receptor is always necessary for structure-based ligand (SBLD) discovery. In other words, is the existence of active state GPCR structures a prerequisite for a successful SBLD program?

GPCRs respond to a broad spectrum of extracellular signals, and depending on the signal they undergo conformational changes upon activation. In turn, these changes are coupled to the activation of cytoplasmic G proteins, β-arrestins, and other effectors, thus inducing cascades of intracellular responses [2,3]. GPCRs exist in a number of conformational states ranging from inactive (R) to active (R*). It is believed that agonists preferentially stabilize the active state, contrary to antagonists which bind to the ground state R. Nevertheless, if the population of R* is high enough, these receptors can actually activate G proteins in the absence of a ligand (basal activity). In summary, there is conformational heterogeneity of these receptors.

Based on the preceding paragraph, an inhibitor occupies the space that would otherwise be taken by an agonist and in turn reduces activity. Therefore, the ground state crystal is sufficient to study GPCR-inhibitor complexes. A compound being designed as an inhibitor is not linked to the signaling events following agonist binding neither does it require an activated GPCR receptor structure? Given that a great number of drugs tend to be inhibitors, a ground state crystal structure would suffice for many pharmaceutical programs. Maraviroc, tiotropium, doxepin, carvedilol are approved drugs acting as antagonists, whose complexes with the respective GPCRs have been resolved [4].

On the other hand, to obtain an active-state model is undoubtedly a formidable task. Protein crystallography of GPCRs remains challenging due to: 1) Instability when these membrane-bound receptors are isolated from the membrane; 2) Conformational heterogeneity of the ligand-receptor complexes stemming from either low affinity ligands and/or high off-rates; 3) The flexibility of the third intracellular loop, which has led to some substitutions in order to attain a more rigid domain [2,5-7]. Consequently, successful crystallization requires innovative techniques such as a stabilized nanobody mimicking the G-protein or covalent binders [5].

Furthermore, even after obtaining an active receptor-G protein complex, another challenge is posed in deciphering where it falls in the whole trajectory of the activation process. Specifically, binding of an agonist causes conformational changes to the receptor which result in regulating the associated G-protein (GDP-bound Gαβγ heterotrimer) by an exchange of GTP for GDP and its subsequent dissociation into the Gα-GTP and Gβγ subunits. The two subunits then impact downstream signaling. It was stated that the active state of a GPCR is the conformation coupled to a nucleotide-free G protein [7]. However, a nucleotide-bound G protein is the prerequisite for the GDP-GTP exchange and the trigger for effector modulation. Thus, the presence of a nucleotide is related to activation and subsequent function from a physiological perspective.

In summary, we should be mindful of the objective in a drug discovery program. If we are seeking to understand structure-function relationships, then active-state crystals are essential. In this context, the GPCR conformational spectrum, including several partial and fully activated state conformations, becomes relevant. The added challenge is to annotate the level of activation once the crystal structure is resolved, which is not straightforward. However, ground state structures are invaluable in structure-based inhibitor design programs, thus lending to success of SBLD simply because an active-state is not always necessary for drug discovery.

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