ACS Local Section
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Adopting NMR spectroscopy to address the dynamic aspects of G protein-coupled receptor (GPCR) activation

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Date: **Thursday April 25th, 2024**
Time: 12:00 pm ET via Microsoft Teams

Abstract

X-ray crystallography and cryo-EM have established a detailed picture of the G protein-coupled receptor (GPCR) structural landscape – laying the foundation for understanding receptor activation in terms of the induced fit and conformational selection models of allostery. Yet, in many instances these conceptualizations remain unsatisfactory for explaining the molecular mechanisms of partial agonists, allosteric modulators and biased agonists. The dynamically-driven model of allostery posits that fluctuations about the mean conformation, which do not produce structural changes on a scale observable by cryo-EM and X-ray crystallography, are sufficient to lower the energy barrier between inactive and active modes. NMR can report on entropically-driven allosteric mechanisms; yet, technical challenges have largely limited its application to the super-microsecond motional regimes of GPCRs. Focusing on a thermostabilized peptide-binding GPCR, the neurotensin receptor 1 (NTS1), we employed NMR and density functional theory (DFT) to probe global sub-microsecond motions of $^{13}C^{\varepsilon}$-methionines. Using this approach, we establish that the NTS1 solution ensemble includes substates with lifetimes on several discrete timescales. The longest-lived metastable states reflect those captured in agonist- and inverse agonist-bound crystal structures separated by large energy barriers. Individual methionine residues, some distributed up to 32 Å apart, also sense rapid motions superimposed within these long-lived states. We observe that the degree of fast, global dynamics correlates with ligand pharmacology. Our results suggest a role for sub-microsecond dynamics and conformational entropy in GPCR ligand discrimination. This approach sidesteps the isotopic labelling limitations imposed by eukaryotic expression systems. We're actively testing the generalizability of our results to the GPCR superfamily and working to understand the underlying mechanism of methionine-based order parameters.

Connection Information

This will be a virtual meeting hosted via Microsoft Teams. A direct link to the meeting is located HERE.

Further information can be found on the NMR Topical Group website.

Please reach out to Christine Jorge (christine.jorge@bms.com) or Rongfeng Zheng (rongfeng.zheng@bms.com) with any questions.

Presented by the NMR Topical Group – North Jersey ACS