MAR14-2014-020941

Abstract for an Invited Paper
for the MAR14 Meeting of
the American Physical Society

Conformational Fluctuations in G-Protein-Coupled Receptors

MICHAEL F. BROWN, University of Arizona

G-protein-coupled receptors (GPCRs) comprise almost 50% of pharmaceutical drug targets, where rhodopsin is an important prototype and occurs naturally in a lipid membrane. Rhodopsin photoactivation entails 11-*cis* to all-*trans* isomerization of the retinal cofactor, yielding an equilibrium between inactive Meta-I and active Meta-II states. Two important questions are: (1) Is rhodopsin is a simple two-state switch? Or (2) does isomerization of retinal unlock an activated conformational ensemble? For an ensemble-based activation mechanism (EAM) [1] a role for conformational fluctuations is clearly indicated. Solid-state NMR data together with theoretical molecular dynamics (MD) simulations detect increased local mobility of retinal after light activation [2]. Resultant changes in local dynamics of the cofactor initiate large-scale fluctuations of transmembrane helices that expose recognition sites for the signal-transducing G-protein. Time-resolved FTIR studies and electronic spectroscopy further show the conformational ensemble is strongly biased by the membrane lipid composition, as well as pH and osmotic pressure [3]. A new flexible surface model (FSM) describes how the curvature stress field of the membrane governs the energetics of active rhodopsin, due to the spontaneous monolayer curvature of the lipids [4]. Furthermore, influences of osmotic pressure dictate that a large number of bulk water molecules are implicated in rhodopsin activation. Around 60 bulk water molecules activate rhodopsin, which is much larger than the number of structural waters seen in X-ray crystallography, or inferred from studies of bulk hydrostatic pressure. Conformational selection and promoting vibrational motions of rhodopsin lead to activation of the G-protein (transducin). Our biophysical data give a paradigm shift in understanding GPCR activation. The new view is: dynamics and conformational fluctuations involve an ensemble of substates that activate the cognate G-protein in the amplified visual response.

[1] A. V. Struts et al. (2011) *Nat. Struct. Mol. Biol.* **18**, 392.
[2] A. V. Struts et al. (2011) *PNAS* **108**, 8263.
[3] M. Mahalingam et al. (2008) *PNAS* **105**, 17795.
[4] M. F. Brown (2012) *Biochemistry* **51**, 9782.