

4CF15-2015-000293

Abstract for an Invited Paper
for the 4CF15 Meeting of
the American Physical Society

Biophysics of G-Protein-Coupled Receptor Activation in Membranes¹

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G-protein-coupled receptors (GPCRs) comprise almost 50% of all pharmaceutical drug targets and afford enormous opportunities in biophysics. Here the visual protein rhodopsin is an important prototype and occurs naturally in lipid membranes. Photoactivation of rhodopsin entails 11-*cis* to all-*trans* isomerization of the bound retinal cofactor, yielding equilibrium between inactive Meta-I and active Meta-II states. We are employing solid-state nuclear magnetic resonance (NMR) spectroscopy as a powerful method to study rhodopsin activation in a membrane lipid environment [1]. For aligned membranes containing rhodopsin, the solid-state ²H NMR lineshapes of the retinal cofactor determine its average conformation and orientation bound to the protein. Solid-state NMR data together with theoretical molecular dynamics (MD) simulations detect increased local mobility of retinal upon light activation [2]. The resulting changes in local dynamics of the cofactor initiate large-scale fluctuations of transmembrane helices that expose recognition sites for the signal-transducing G-protein. Moreover the lipids and water comprise the so-called "dark matter" of cellular membranes. Effects of membrane lipids on G-protein-coupled receptors (GPCRs) are revealed by UV-visible and FTIR spectroscopic studies of how they govern the conformational energetics of rhodopsin in visual signaling [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]. The new biomembrane model challenges the standard fluid mosaic model. The FSM describes elastic coupling of membrane lipids to the conformational energetics of rhodopsin. Additional influences of osmotic pressure dictate that a large number of bulk water molecules are implicated in rhodopsin activation. An ensemble-mediated activation mechanism is proposed for rhodopsin in a natural membrane lipid environment, which includes a role of bulk water in the activation of rhodopsin-like GPCRs [4]. Ion channels, transporters, and membrane-bound peptides are all affected by elastic deformation of the bilayer, thus giving a new paradigm for membrane lipid-protein interactions in structural biophysics. [1] A. V. Struts et al. (2011) *PNAS* **108**, 8263. [2] N. Leioatts et al. (2014) *Biochemistry* **53**, 376. [3] M. Mahalingam et al. (2008) *PNAS* **105**, 17795. [4] M. F. Brown (2012) *Biochemistry* **51**, 9782.

¹Research supported by NIH.