Gobind Khorana and the "Central Dogma" of Receptor Activation

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G-Protein Coupled Receptors (GPCRs) are the input stages to biochemical transducers that mediate environmental signals and cellular responses. Rhodopsin, the photoreceptor of the retina, was the first GPCRs to be characterized, and has remained a paradigm for what is now recognized as one of the largest superfamilies of proteins. The construction and expression of a synthetic gene for rhodopsin by Oprian and Khorana paved the way for biophysical studies that revealed key features of the mechanism by which rhodopsin transduces a photon of light into a structural change recognized by other proteins ("activation"). One of the biophysical techniques was Site Directed Spin Labeling (SDSL), which, when employed in collaboration with Khorana's group, revealed a remarkably simple molecular change underlying activation; a rigid-body motion of one of the 7 transmembrane helices that make up the protein. Qualitatively, this motion has been confirmed in many GPCRs, and is viewed as a unifying theme of receptor activation. New technologies in SDSL revealed quantitative details of the activating structural change, and subsequent crystal structures published during the last year confirm in remarkable detail the nature of the change. But the crystal structures miss an interesting point, namely the extremely high flexibility of the receptor recognition interface; apparently nature uses disorder, and a frontier in receptor biophysics is to understand how.