

Structure and activation of the LH receptor

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Introduction: The human genome contains over 800 genes encoding G protein-coupled receptors, a number of which have relatively large N-terminal ectodomains (ECDs). The glycoprotein hormone receptors belong to this latter class, each having ECDs responsible for specific high affinity hormone binding and characterized by a leucine-rich-repeat (LRR) structure capped by cysteine-rich regions. Ligand binding to the ECD leads to a conformational change in the receptor transmembrane region (TMR) and subsequent G protein coupling. The goals of this project are to delineate the molecular basis of hCG-LH receptor (LHR) binding and the nature of receptor activation and G protein binding/activation. **Methods:** Experimental approaches have involved site-directed mutagenesis of LHR, protein engineering to achieve fusion proteins of hCG and LHR (ECD and full-length), mass spectrometry, CD spectroscopy, surface plasmon resonance studies, and transfections of HEK 293 cells followed by binding and signaling studies. In addition, computational approaches (homology modeling and molecular dynamics simulations) were used to develop models and guide the design of structure-function studies. **Results:** Homology modeling with several proteins of known crystallographic structure has yielded a tentative structure of much of LHR, including most of the ECD and a significant portion of the TMR. Likewise, a combination of homology modeling and structure-function studies, based on site-directed mutagenesis, has provided a model for the hCG-LHR ECD complex in which both subunits of hCG contact multiple LRRs. A combination of homology modeling and structure-function studies using naturally occurring and engineered mutations has led to a model for receptor activation in which the cytosolic extensions of helices 3 and 6 become more solvent accessible, presumably facilitating G protein binding/activation. Several amino-acid residues in the cytosolic extensions of helices 3, 5, and 6, as well as the N-terminal half of intracellular loop 2 have been mapped as critical in this process. **Conclusions:** Working models are now available for structures of the hCG-LHR ECD complex and of the inactive and active forms of the TMR. Major questions remaining are the molecular nature of the modes of hCG-LHR ECD-TMR interaction and of the activated TMR interaction with the G protein. Supported by NIH DK33973 and DK69711.