

Structure of FSH in complex with the hormone-binding domain of FSHR

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Crystal structures are known for the human glycoprotein hormones CG and FSH, and the glycoprotein hormone receptors belong to a family of leucine-rich repeat G-protein coupled receptors (LGRs). Numerous studies show that glycoprotein hormones bind with high affinity and high specificity to the leucine-rich repeat ectodomains of their cognate receptors and that receptor binding is largely separable from the receptor activation that leads to cAMP production.

We produced a recombinant human FSH:FSHR_{HB} complex through secretion from insect cells that had been infected with a baculovirus vector constructed to encode both an FSH β -FSH α fusion protein and a hormone-binding portion of the FSHR ectodomain (FSHR_{HB}). Thin crystals were grown by vapor diffusion after partial deglycosylation (~20%) of the purified complex, and the structure was determined at 2.9Å resolution by x-ray crystallography. Dimerization of the hormone-receptor complexes was studied in solution by analytical ultracentrifugation, dynamic light scattering, and chemical cross linking.

FSH binds in a hand-clasp fashion to the curved inner surface of FSHR_{HB}, making contacts with all ten β -strands of the repeat structure. The resulting interface is large (2600Å²) and has a high charge density (1.1 charges per nm²). Specific characteristics of the interface, when considered in the light of comparative sequences and other studies, support universality of this mode of interaction for the family and provide an explanation for the specificity with which glycoprotein hormones bind to their receptors. Receptor-induced conformational changes in the hormone and the geometry of hormone presentation in the complex inspire hypotheses concerning the mechanism of transmembrane signal transduction. Characteristics of the dimeric structure and the expected enhancement of intrinsic affinity ($K_d \approx 400\mu\text{M}$ for free complexes) when ectodomains are tethered to the membrane suggest that such dimers may have functional consequences.