



## Structure-Function Correlates of Human FSH

**Ilpo Huhtaniemi**

Department of Reproductive Biology, Imperial College London, Hammersmith Campus,  
Du Cane Road, London W12 0NN, UK (E-mail: [ilpo.huhtaniemi@imperial.ac.uk](mailto:ilpo.huhtaniemi@imperial.ac.uk))

The prevailing concept about the function of follicle-stimulating hormone (FSH) is that one hormone molecule binds to one FSH receptor (R) molecule, a member of the G-protein coupled receptor (GPCR) family. The interaction activates through G<sub>s</sub> protein adenylyl cyclase to catalyse production of the second messenger, cAMP, which then triggers an array of intracellular responses. In real life, however, there are many pleomorphic features in this cascade, determined by subtle structural variations in FSH and FSHR molecules, structurally and functionally different conformations of hormone-receptor complexes, multiple signaling mechanisms, and extragonadal actions of FSH.

Apart from several known mutations inactivating FSH or FSHR function (1,2), the FSH $\beta$  gene is structurally well conserved, and functionally significant polymorphisms are not known (3). FSHR has polymorphisms that have been shown to affect ovarian sensitivity to FSH stimulation (4), and FSHR exists as several splice variants, some of which are expressed as growth factor/cytokine receptor-like proteins with a single transmembrane domain (5). It is proposed that a different array of FSH actions is mediated through these alternative receptors. Important heterogeneity in FSH function is caused posttranslationally by the variability in the glycosylation of circulating FSH molecules, which affects both the circulatory half-life and bioactivity of the hormone (6). Alkaline forms of FSH are more bioactive at the receptor site in vitro, and acidic forms have longer half-life in vivo. In addition, different FSH isoforms may activate different signaling cascades. The isoform distribution shows specific changes around the menstrual cycle, which may indicate qualitative differences in FSH action according to the functional state of the ovary. There is pleomorphism also in FSHR binding, since in addition to the one ligand-one receptor cis-activation model, trans-activation through formation of dimers or higher order hormone-receptor oligomers has been shown in vitro, but not yet in vivo, to diversify the receptor signaling. There is some in vitro evidence that monomeric and di/oligomeric FSHR activation triggers different signaling mechanisms (7). With respect to FSH-FSHR dimerisation, the exact conformation of the complex is still debated (8-10). Besides the classical cAMP mediated signaling, also the inositol trisphosphate, Ca<sup>++</sup> and MAPK pathways can be activated upon FSH stimulation (11,12). Whether distinct functional responses are triggered by the different signaling mechanisms and whether the different FSH isoforms prefer specific intracellular responses also remains unknown. Finally, FSHR is expressed also in several extragonadal tissues and it is possible that its actions are not limited to the ovary and testis. The involvement of direct FSH action in prostatic function (13) and postmenopausal osteoporosis have been recently proposed (14).

In conclusion, FSH functions show pleomorphism at multiple levels, including the hormone and receptor structure and function, the signaling cascades involved, and the array of FSH target cells and organs. The possibility to amplify the desired actions and/or to eliminate the undesirable ones poses an interesting challenge for the development of novel pharmacological FSH preparations.



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Department of Reproductive Biology, Imperial College London, Hammersmith Campus,  
Du Cane Road, London W12 0NN, UK (E-mail: [ilpo.huhtaniemi@imperial.ac.uk](mailto:ilpo.huhtaniemi@imperial.ac.uk))

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